PRIMARY INTRACEREBRAL HÆMORRHAGE
RESULTS OF SURGICAL TREATMENT IN 244 CONSECUTIVE CASES

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DURING the past ten years neurosurgeons have become progressively more interested in the problem of ruptured intracranial aneurysm, and, as a result, many more patients with acute cerebrovascular accidents have found their way to neurosurgical departments. The difficulties of purely clinical diagnosis in these conditions are well known, and it is hardly surprising that many patients admitted as cases of "subarachnoid hæmorrhage" have been shown by ancillary diagnostic methods to have cerebral hæmorrhage, thrombosis, embolism, &c.

A recent review of our cases presenting with "subarachnoid hæmorrhage" illustrates this point well:

Diagnosis	*No. of cases*
Arterial aneurysms	1183
Angiomas	183
Cerebral or cerebellar haemorrhages	278
No lesion seen by angiography	472
Total no. of cases	2116

In these cases more than 13% of such cerebrovascular accidents were caused by spontaneous primary intracerebral or intracerebellar hæmorrhage. Whilst a few patients may have bled from a minute angiomatous malformation, which disintegrated at the moment of rupture, most will have ruptured an atherosclerotic vessel.

We do not suggest that the figure of 13% indicates the true incidence of primary hæmorrhage in the whole field of cerebrovascular accidents, for the majority of our patients had been selected for admission by the sending hospitals. It must also be remembered that over 20% of patients with primary intracerebral hæmorrhage do not have blood in the cerebrospinal fluid (C.S.F.).

In this paper we describe a consecutive series of 244 cases of primary intracerebral hæmorrhage admitted under the care of one of us (W. McK.) to the National Hospital, Queen Square, or to Atkinson Morley's branch of St. George's Hospital.

These were partly derived from the 278 cases mentioned above, after excluding 28 cases of spontaneous intracerebellar hæmorrhage (which form the subject of a separate paper [McKissock, Richardson, Walsh 1959]), those due to trauma, neoplasm, and systemic disease, and also patients with primary pontine hæmorrhage, thus providing 179 cases of primary intracerebral hæmorrhage presenting as subarachnoid hæmorrhage. To these were added 65 cases in which the C.S.F. was clear or the findings at lumbar puncture doubtful. The diagnosis in all 244 cases was proved at either operation or post mortem.

Present Series

Age-incidence

Most patients (i.e., 91%) had their hæmorrhage between the ages of forty and seventy years:

Age (yr.)	20–29	30–39	40–49	50–59	60–69	70+
No. of cases	6	15	59	90	54	20

This incidence is similar to that reported by David and Hécaen (1945), but rather higher than that in the series described by Werner (1954). The low incidence in the last two age-groups is almost certainly due to selection at the admitting hospitals, and perhaps also to natural selection by rapid death of these older patients.

124 patients were male and 120 female. This agrees with the figures quoted by Dalsgaard-Nielsen (1955) and does not show the greater preponderance of men as reported by Werner (1954).

No correlation between occupation and hæmorrhage was evident, again in agreement with Dalsgaard-Neilsen (1955). Historical details were lacking in many cases, the patients having been found unconscious in a variety of situations. In only 118 was it possible to establish the conditions under which the episode took place. Because 58 patients were active at the time of the ictus, whilst 60 were at rest, this does not seem to be a relevant factor in causation.

Hypertension was certainly present in 152 cases, and equally certainly absent in 57, whilst there was some doubt as to its existence in 35 patients who were moribund on admission.

Mode of Onset

The generally accepted picture of sudden onset with headache and vomiting, rapidly followed by the development of neurological signs and depression of consciousness, is well known. But we shall show that more than half the patients did not present in this way, many retaining consciousness initially, whereas in others the onset was ingravescent: some or all of the usual symptoms may be absent, the neurological signs may be inconclusive and blood may be absent from the C.S.F. The distinction between hæmorrhage and thrombosis is therefore far from easy on clinical grounds alone (Kelly 1958).

The mode of onset in these 244 cases can be divided into four main clinical groups:

I. Sudden onset *without* loss of consciousness (89 cases).
II. Sudden onset *with* loss of consciousness (117 cases).
III. Gradual onset *without* loss of consciousness (23 cases).
IV. Gradual onset *with* later loss of consciousness (3 cases).

Because the remaining 12 patients had been living alone and were admitted to hospital already in coma, the mode of onset was unknown.

Thus, almost half the patients were never unconscious. Of those conscious at the onset 26 later lost consciousness, 19 within forty-eight hours, and 7 within three to five days. Of those rendered unconscious initially 31 regained consciousness, 18 within forty-eight hours and 13 in three to five days. These facts illustrate the variation in the development of the clinical picture, and the different courses that primary intracerebral hæmorrhage may take.

Clinical State on Admission

As would be expected most of these patients (187 of the 244) presented with hemiparesis or a frank hemiplegia. Using the grouping mentioned earlier with regard to the mode of onset, a brief outline of the neurological state of the patients may be given:

Group I (89 cases).—No less than 73 had developed a hemiplegia or hemiparesis, 29 of them with an associated hemianopic field defect but no sensory loss, 11 with similar field defect

and also sensory loss, and 6 with sensory loss but no field defect. 9 patients presented with confusion alone, whilst 7 were in coma.

Group II (117 cases).—26 patients were in deep coma, and 60 were unconscious but responding to pain, these responses suggesting a hemiplegia in all cases, with associated sensory loss in 9. Of the 31 who regained consciousness, 15 had sensory loss and a hemianopia in addition to a hemiplegia, and 15 had an additional hemianopia but no sensory signs. The remaining patient presented with confusion alone.

Group III (23 cases).—20 had a hemiplegia or hemiparesis, of whom 6 had in addition a hemianopia but no sensory signs, 4 had a field defect with sensory loss, and 2 had sensory loss without hemianopia. 2 patients presented with confusion alone, and 1 with a field defect alone. 3 patients in this group had papillœdema.

Group IV (3 cases).—1 patient was admitted with hemiplegia, cortical sensory loss, and a hemianopic field defect, 1 had a hemiparesis only, and the 3rd had a hemiplegia and hemianopic field defect but no sensory loss.

Presence of Blood in the Subarachnoid Space

In 201 of the 244 patients a lumbar puncture was performed. Fresh blood was found in 161, no blood was revealed in 39, and in the remaining patient the result was dubious. In the 43 patients not subjected to lumbar puncture the ventricular fluid was xanthochromic or bloodstained in 18, and clear in 9. In the other 16 cases there was doubt because the interval from the ictus was long, or because the blood might have been due to needling of the ventricle.

Thus in 179 cases the C.S.F. indicated recent hæmorrhage, in 48 it did not, and in 17 there was doubt. In over 20% of the patients, therefore, the C.S.F. was clear and colourless, although in some of these the protein content of the fluid was raised, and in 5 others a pleocytosis led to the patients being treated as cases of meningitis (Bedford 1958).

Investigations

In pursuance of our policy regarding early treatment of ruptured intracranial aneurysms (McKissock and Walsh 1956), angiography was performed on all patients with subarachnoid hæmorrhage. This was done as soon as possible after admission to hospital and clinical examination, and when carotid compression in the neck had confirmed the relative safety of the procedure. The investigation was omitted where the patient's clinical state was such as to demand immediate exploratory burr-holes as an attempted lifesaving measure.

In those cases where a cerebrovascular accident was suspected on clinical grounds although blood had not been demonstrated in the C.S.F., the same procedure was followed. There were in addition 15 cases in which the onset and course were atypical, the true nature of the lesion being discovered only during ventriculography or craniotomy.

Angiography was carried out in 167 of the 244 patients, unilaterally when the hæmatoma was at once revealed, but bilaterally in cases of doubt or difficulty.

In 114 patients a space-occupying lesion was shown, and in 53 the angiograms were within normal limits.

6 patients, all of whom were unconscious and deteriorating at the time of angiography, died immediately after the investigation. In 3 of them angiography had given positive results, confirmed post mortem, but the other 3, with negative angiograms, also showed hæmorrhages at necropsy.

Of the 53 patients with negative angiograms, 22 had had disruptive hæmorrhages involving the basal ganglia, and in 31 significant hæmatomas were removed at subsequent operation. The accuracy of angiography was thus a little less than 70%.

Exploratory posterior parietal burr-holes were considered necessary (1) to localise the hæmorrhage in cases where angiography had merely shown which side the lesion was on; (2) to demonstrate hæmorrhage in clinically suggestive cases where the angiogram was normal; or (3) in cases too urgent for angiography.

In 60% a hæmatoma was encountered by the exploring cannula, and the lesion was localised; in other cases air injection was required for this purpose. We were thus able to demonstrate with considerable accuracy which space-occupying hæmatomas in the cerebral and cerebellar hemispheres were amenable to surgical intervention.

Surgical Treatment

12 patients died before surgery could be undertaken, whilst 1 patient seemed to be recovering so well that surgical intervention was contraindicated.

The methods of surgical treatment employed were:

	No. of cases
Ventricular tapping alone	9
Ventriculography alone	14
Burr-hole exploration and evacuation of hæmatoma	104
Burr-hole aspiration of hæmatoma with subsequent craniotomy	73
Craniotomy for evacuation of hæmatoma	31

Aspiration of blood through a burr-hole was felt to be indicated in those patients in danger of dying from cerebral compression caused by the hæmorrhage, but it was used also where the hæmatoma was not localised by angiography. In these latter cases the hæmatoma was encountered during the preliminary stages of ventriculography, air injection proving unnecessary. In the earlier cases in this series treatment by burr-hole aspiration or by immediate elective craniotomy was used with about equal frequency, but in the more recent cases the tendency has been to aspirate as much liquid blood as possibe and then to remove the remainder by craniotomy after forty-eight hours or more.

Results of Surgery

231 of the 244 patients in this series remain for assessment of the results of surgical intervention:

	No. of patients	*No. of deaths*	
Ventricular tap alone	9	9	
Ventriculography alone	14	11	(2 improved but died later; 1 alive with moderate disability)
Definitive surgery	208	106	

Surgical deaths included all patients not surviving three weeks after operation.

Of the 208 patients receiving definitive surgery (burr-hole aspiration, elective craniotomy, or both) there were initially 102 survivors. The follow-up period varied from one to ten years, with an average of two years. Of these 102 survivors 31 have since died.

Improved by surgery:	
From further cerebrovascular accident	4
From other known causes	6
From unknown causes	4
Total	14
Unimproved by surgery:	
From progression of disease in periods of 1–3 mos.	10
From further cerebrovascular accident	1
From other known causes	1
From unknown causes	5
Total	17

8 patients were lost in follow-up, and the 63 survivors are in various degrees of health. They were regarded as "well" if able to return to full employment or household duties, "minimally disabled" if only able to do part-time or light work, "moderately disabled" if unemployed, and "totally disabled" if unable to lead an independent existence:

Well	25
Minimal disability	14
Moderate disability	18
Disabled	6
Total	63

Thus of the entire series of 244 patients there are 63 known survivors. The overall mortality is 74% and the operative mortality 51%.

Factors Influencing Mortality

Age appears to have little influence upon survival apart from the "70 +" group. Thus age of itself is no bar to surgery.

The following table shows the age-distribution of the 140 patients who died:

Age (yr.)	20–29	30–39	40–49	50–59	60–69	70+
No. of deaths	3	7	30	53	31	16
Total no. of cases	6	15	59	80	54	20
Mortality (%)	50	45	42	55	57	80

Situation and Size of Hæmorrhage

The considerable variation in the sites of the hæmorrhagic lesions in these patients is best illustrated by the following table:

—	Frontal	Fronto-parietal	Fronto-temporal	Parietal	Parieto-temporal	Parieto-occipital	Temporal	Temporo-occipital	Capsular	Hemisphere
Total no.	30	17	9	41	19	7	51	3	56	10
No. of deaths	10	10	3	14	7	7	21	1	52	9
Mortality	33%	59%	33%	34%	37%	100%	41%	33%	93%	90%

A larger lesion does not in itself mean greater risk. It seems that deeply placed disruptive hæmorrhages involving the internal capsule, basal ganglia, and ventricular system, even though small, carry a devastatingly high death-rate from associated damage to vital centres. The other type of lesion, in which the fibre tracts appear to be split by the hæmorrhage, seems to be more amenable even when it is large, and offers a much better chance of recovery of neurological function if the patient survives both hæmorrhage and operation. In such cases quite dramatic improvement in focal signs may follow removal of the clot. Another factor, of course, is the degree of cerebral swelling associated with these different types of hæmorrhage.

Hypertension, on the other hand, seems to have an unfavourable influence, for among 152 hypertensive patients there were 89 early deaths (58%), whilst among the 57 normotensives there were only 20 (35%). The death-rate in the dubious group, where the state of the blood-pressure was not certainly known, was much higher; but this was hardly surprising since nearly all these patients were moribund on admission. On these figures, therefore, the presence of hypertension seems to worsen the prognosis; but this is partly because the grave disruptive hæmorrhages involving the basal ganglia and ventricular system occur predominantly in hypertensive patients. There were 52 such cases of capsular hæmorrhage, and, if these be subtracted from the hypertensive group, the mortality for this group becomes 37% (100 patients with 37 early deaths). This is still a high mortality but an acceptable one for the surgical treatment of such a lethal disease. From our experience so far, and that of Klein and Ballantine (1958), it seems that disruptive capsular hæmorrhages produce so much intrinsic brain damage at the time of rupture that surgery will never be of any avail.

The state of consciousness at the time of proposed operation, and hence also the way the clinical picture develops, seems undoubtedly to affect the outcome of surgical treatment. When our patients are regrouped according to their conscious state at the time of operation, a steady rise in death-rate is seen to follow deterioration in the level of consciousness:

	No. of cases	*No. of deaths*
Alert	58	13 (23%)
Drowsy	98	45 (46%)
Stuporose	32	24 (75%)
Coma	56	56 (100%)

This steady increase in death-rate as the level of consciousness decreases must surely be significant; it emphasises the desirability of early investigation and treatment, when the initial ictus is not overwhelming, in an effort to avoid progressive brain damage. It seems desirable also to make a rather different assessment of the patients, correlating the time after the ictus with the level of consciousness in the hope of improving the timing of surgical intervention.

We have attempted to assess the different forms of surgical treatment employed, grouping the patients according to their states of consciousness:

Burr-hole aspiration alone:

	No. of cases	*No. of deaths*
Alert	24	5 (21%)
Drowsy	39	26 (66%)
Stuporose	18	16 (90%)
Coma	23	23 (100%)
Total	104	70

Craniotomy and evacuation of clot:

	No. of cases	*No. of deaths*
Alert	13	0 (0%)
Drowsy	15	6 (40%)
Stuporose	1	1 (100%)
Coma	2	2 (100%)
Total	31	9

Burr-hole aspiration followed by craniotomy:

	No. of cases	*No. of deaths*
Alert	16	3 (19%)
Drowsy	37	12 (32%)
Stuporose	16	8 (50%)
Coma	4	4 (100%)
Total	73	27

Although the individual groups are too small for statistical analysis it seems that elective craniotomy alone produces better results in the "alert" group, and that all forms of surgical treatment of the "stuporose" and "coma" groups (66 patients with 56 deaths) have been singularly unsuccessful. (See also Odom et al. 1952, Gomensoro and Arana 1957, Howell 1957, Klein and Ballantine 1958.)

Discussion

This series of surgically treated patients cannot, of course, be compared with any reported group treated conservatively, largely because it is composed entirely of verified cases of intracranial hæmorrhage presumably

due to arteriosclerosis. The diagnosis of cases treated conservatively must rest upon clinical grounds or post-mortem evidence. In " recovered " cases the lesion is a matter of clinical impression, as in the many reports of the conservative treatment of so-called subarachnoid hæmorrhage. It is equally difficult to compare our cases with other surgically treated cases for our series has been consecutive and entirely unselected by us, no patient being deemed too ill for investigation and treatment although many were moribund on admission.

Considering the gravity of the disease, a survival of only 65 out of 244 is not perhaps as disappointing as it may appear; but it should certainly stimulate neurosurgeons to a deeper interest in this challenging problem.

In this paper we have reviewed what has been achieved in the past, largely with the idea of planning our investigations and design for the future. A number of facts emerge, of which the most important is probably the lack of a series of comparable cases, treated by conservative means alone, against which to assess the advantages or disadvantages of surgical methods of treatment. The accuracy of 70% offered by angiography in the diagnosis of these lesions is too imprecise, and it is obviously desirable that some other diagnostic measure, short of surgical intervention, should be devised. Because the mere introduction of a brain cannula into a hæmatoma cavity may well alter the prognosis, this means could hardly be used to establish the diagnosis of hæmorrhage in a series of cases designed to be treated medically. A single method of surgical treatment should be chosen which can be used in a random set of patients and assessed against a similar series treated conservatively.

Further, the metabolic effects of these lesions require additional study: we know little of the general disturbances occasioned by the ictus or of the local alterations in the C.S.F., although both these factors may militate against a successful outcome. Whilst not losing sight of the desirability of removing a space-occupying hæmatoma, we must not ignore these secondary metabolic disturbances which may rob us of surgical success. Much work has been done on similar problems in cases of head injury (Tower and McEachern 1949a and b, Higgins 1954), in epileptics (Tower and McEachern 1949a and b), and in patients submitted to cranial surgery (*Lancet* 1958), but little has been done in the field of intracerebral hæmorrhage. Cerebral anoxia produced by congestion, unconsciousness, and the accumulation of secretions in the nasopharynx and trachea, must play a part in the deterioration of these patients, and it may well be made worse by angiography. We feel that early tracheostomy has its place in treatment, possibly even before radiological investigations; for it has certainly proved its worth as a postoperative measure in cerebral surgery, and in the treatment of severe head injuries.

In the coming years we hope to assess surgical methods of treatment as against active conservative measures, due consideration being given to the history, clinical state, and modes of investigation in relation to age, sex, hypertension, state of consciousness, and time since the ictus.

Summary

A consecutive series of 244 cases of proven primary intracerebral hæmorrhage is reported.

The absence of blood in the lumbar or ventricular fluid in 20% of these cases is noted in relation to the difficulties of of purely clinical diagnosis.

The factors influencing mortality are: (1) the site but not the size of the lesion (capsular hæmorrhages carrying the worst prognosis), (2) hypertension, which is unfavourable, and (3) the state of consciousness at the time of operation, the death-rate rising as the level of consciousness falls.

The urgent use of ancillary methods of diagnosis (angiography and sometimes exploratory burr-holes) is emphasised.

The various methods of surgical treatment employed are related to the state of consciousness of the patients.

The immediate operative mortality was 51%. Subsequent deaths, from various causes, raised the total mortality to 74%.

Of the 63 survivors 25 are well, and only 6 are totally disabled.

Various lines of research are contemplated. There is need for a controlled series of cases treated by conservative measures.

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BENIGN RECURRENT INTRAHEPATIC "OBSTRUCTIVE" JAUNDICE

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MANY disorders with differing clinical and metabolic features are classified as " constitutional hyperbilirubinæmia ". Gilbert and Lireboullet (1901) drew attention to the occurrence of benign non-hæmolytic jaundice without bile in the urine, but it is now considered that several diseases may give similar findings (Foulk et al. 1959), including the group of patients specified by Crigler and Najjar (1952). In addition, a constitutional hyperbilirubinæmia with obstructive features has been described (Dubin and Johnson 1954, Sprinz and Nelson 1954). It is characterised by the presence of bile in the urine and pigment in the hepatic cells, and many further examples have since been recognised (Dubin 1958).

We report here two cases of benign recurrent jaundice with obstructive features, which differ in several essential respects from those summarised by Dubin (1958), and which cannot be classified within the existing nomenclature of liver disease.

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Case-reports

Case 1.—A woman, then aged 29 and in the fourth month of pregnancy, was admitted to the Central Middlesex Hospital in March, 1941, complaining of jaundice, dark urine, pale stools, and itching of two months' duration. Despite termination of the pregnancy and bed rest, the jaundice persisted, and she discharged herself from hospital against advice in June that year. There was a previous history of jaundice lasting nine months after " severe influenza ", when she was 9 years old.

Further lengthy episodes of deep jaundice leading to brief hospital admissions for investigation occurred in October, 1949 (lasting more than six months), September, 1951 (lasting a year), and September, 1956 (lasting two years). On each occasion jaundice, itching, pale stools, and dark urine were present. Her general health was relatively unimpaired, apart from some weight loss, fatigue, and flatulence; there was no fever. Further measures—including laparotomy on two occasions, and bed rest—failed to influence the condition. During the intervening periods jaundice disappeared, stool and urine colour became normal, and, on the one occasion it was measured during a period of remission, the serum-bilirubin concentration was not raised.

Her physique and nutritional state were satisfactory (except after long-continued jaundice); she rarely drank alcohol; and no evidence could be found of exposure to or consumption of drugs. The previous history was otherwise unremarkable, but her father was unknown. No history of jaundice was obtained from her half-brother, her mother, or her 4 surviving children, and serum-bilirubin concentrations below 0·5 mg. per 100 ml. were found in her mother and one of her daughters.

On each occasion that she was jaundiced there was no hepatomegaly, splenomegaly, or other stigma of liver disease. Itching was often followed by papular eczema with secondary infection and furunculosis. Occasionally she had epistaxis or bruising of the skin after long periods of jaundice. Xanthomata and xanthelasma were never present.

Case 2.—A man, now aged 33 years, first experienced jaundice at the age of 17. Subsequently he has had sixteen further attacks, varying in duration from one to six months. Each time the disorder has been characterised by a brief episode of vomiting, followed by the passage of dark urine and pale stools, and the subsequent development of progressive jaundice and itching. He has been admitted to hospital seventeen times, and laparotomy has been performed during periods of jaundice on four occasions. There has been no fever or other constitutional disturbance, apart from weight loss, on any occasion. He seldom drinks alcohol; there is no evidence of exposure to or consumption of drugs or other agents known to cause jaundice; and he has no family history of consanguinity or jaundice.

Physical examination has always shown jaundice and scratch marks without evidence of hepatomegaly, splenomegaly, or other signs of liver disease. After lengthy episodes of jaundice there has occasionally been bruising of the skin which has responded to vitamin-K injections, but xanthomata and xanthelasma have never developed.

Clinical Findings and Results of Investigations

Nutrition

Weight loss occurred during periods of deep jaundice in both patients, and was presumably due to intestinal malabsorption as the stool fat content in case 1 during an attack of jaundice (December, 1949) was 66·4% of the dry fæcal weight. In October, 1951, at the onset of jaundice, her weight was 200 lb. (90·9 kg.). It decreased to 150 lb. (68·2 kg.) by May, 1952, but subsequently improved to 180 lb. (81·8 kg.) after recovery in November of the same year. In September, 1958, after a further period of jaundice, her weight had fallen to 136 lb. (61·8 kg.). Weight loss also occurred during jaundice in case 2, 22 lb. (10 kg.) being lost during a two-month attack in 1948.

TABLE I—BIOCHEMICAL FINDINGS (HIGHEST AND LOWEST RECORDED VALUES)

—	Serum-bilirubin (mg. per 100 ml.)	Serum-alkaline-phosphatase (K.A. units per 100 ml.)	Thymol turbidity (units)	Serum-albumin (g. per 100 ml.)	Serum-globulin (g. per 100 ml.)	Urine	
						Bilirubin	Urobilinogen
Case 1	40·0–0·5	34·5–21·0*	0	5·8–3·9	3·7–2·8	+++–0	±
Case 2	38·0–0·5	30·0–19·5*	1	5·9–4·1	2·7–2·1	+++–0	±
Normal range	<1·0	<12	<3	>4·0	<3·0	0	±

* No value available during remission.

The prothrombin-time was usually normal, but it was prolonged during separate episodes of jaundice twice in case 1 (44% and 24% of normal), and thrice in case 2 (74%, 64%, and 17% of normal). This abnormality, together with bruising and epistaxis when present, responded to vitamin-K injections. In case 1, serum-calcium and inorganic phosphate were repeatedly within the normal range, but skeletal radiography after eighteen months' jaundice showed some loss of bone density. There were no subjective symptoms referrable to the skeletal system in either patient.

Liver-function Tests

Biochemical tests of liver function were performed in each attack of jaundice and showed an " obstructive " pattern in both patients (table I). An immediate positive direct van den Bergh reaction was associated with deep, fluctuating jaundice, sometimes reaching serum-bilirubin levels above 35 mg. per 100 ml. in both patients. The serum-alkaline-phosphatase level was always raised during attacks, often exceeding twice the normal, but the serum-cholesterol remained within the normal range (less than 255 mg. per 100 ml.).

Total serum-protein and serum-albumin levels were repeatedly within normal limits, but paper electrophoresis in case 1 showed increases in the α_2 and β globulin fractions. Flocculation tests (thymol-turbidity and cephalin-cholesterol or zinc-sulphate reactions) were consistently negative in both patients. Bile was always present in the urine during attacks, but the relative concentrations of the mono- and di-glucuronides of bilirubin were not measured. The urinary aminoacid patterns in case 2 were unremarkable. During periods of remission there was no clinical evidence of biliary obstruction, while liver-function tests and the results of urinary investigation reverted to normal.

Additional Investigations

Total and differential white-blood-cell counts were normal in both patients on many occasions, and in particular there was never any eosinophilia. On one occasion a slight iron-deficiency anæmia (hæmoglobin 11·5 g. per 100 ml. in March, 1957) was found in case 1, but this responded to iron therapy by mouth and hæmoglobin determinations were otherwise above 13·3 g. per 100 ml. at all times. The reticulocyte-count was never above 1% in either patient, and although urobilinogen was present in the urine it was never excessive. Fæcal urobilin determinations during an episode of jaundice in case 2 had been as low as 8–10 mg. per 100 g. of stool. Red-cell-fragility curves were normal in both patients, while the Wassermann reactions were negative and concentrations of blood-urea and electrolytes showed no abnormality.

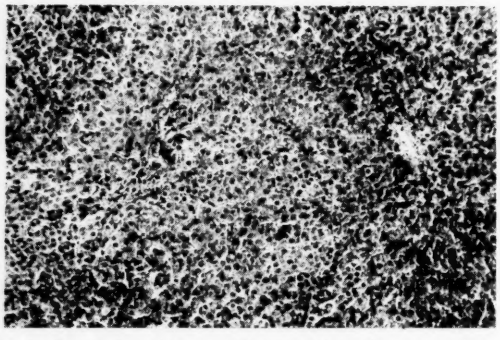

Fig. 1—Case 1: liver biopsy. (Hæmatoxylin and eosin. ×100.)

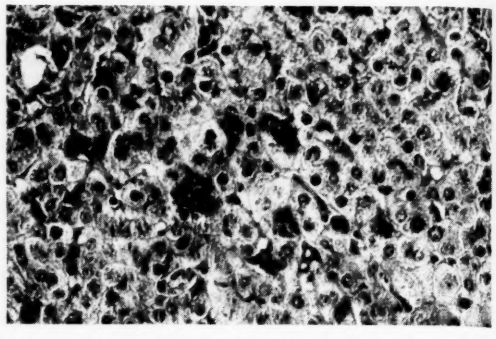

Fig. 2—Case 1: liver biopsy. (Hæmatoxylin and eosin. ×300.)

Radiological and Operative Findings

During periods of remission, when serum-bilirubin levels were not raised, intravenous cholangiography was successful and showed normal appearances of the biliary tree in both patients. In case 2 cholecystography showed the normal concentration of dye and appearance of the gallbladder; while in case 1 inflation of a Miller-Abbott tube at the duodenojejunal flexure, followed by the introduction of barium into the stomach, failed to produce a back-flow of contrast medium into the common bileduct. X-ray films of the stomach and duodenum were normal in both patients.

Laparotomy was performed twice in case 1 and four times in case 2, always during periods of deep jaundice. On each occasion in both patients the naked-eye appearances of the liver and gallbladder were unremarkable and explorations of the bileduct were negative. Adequate surgical cholangiograms were obtained in both patients. The dye flowed easily in both directions, and there was no evidence of dilatation or obstruction of the intrahepatic and extrahepatic biliary system. Bile taken from the gallbladder in case 2 at operation showed no abnormality.

Hepatic Histology

Surgical liver-biopsy specimens during episodes of jaundice were taken twice in case 1 (1951 and 1956), and needle-biopsy specimens on three occasions in case 2 (1945, 1949, and 1957). The appearances were similar and indicated intrahepatic biliary obstruction.

In case 1 distension of the bile canaliculi with bile, slight infiltration of the portal tracts with round cells, and occasional patchy cell necrosis were present (figs. 1 and 2). In case 2 bile stasis in the canaliculi, particularly in the centrilobular region, scattered bile thrombi and isolated necrotic liver cells and patchy round-cell infiltration in the portal tracts were again the prominent features (figs. 3 and 4). No significant duct proliferation or liver-cell necrosis was present in either patient, and in particular there was no abnormal pigment in the liver cells or eosinophilia, nor was there any evidence of cirrhosis or of other alteration in hepatic architecture.

Treatment

Apart from bed rest, laparotomy, and an adequate diet, with the parenteral administration of the fat-soluble vitamins A, D, and K, the only specific therapeutic measures attempted in case 1 were trials of steroid and corticotrophin therapy.

A course of cortisone (200 mg. daily) had been prescribed in 1952, but it was abandoned after seven days because of side-effects and its failure to influence the jaundice appreciably.

In August, 1958, a seven-day course of corticotrophin (60 units daily) was given. Serum-bilirubin concentrations before and after a five-day control period were 4·0 mg. per 100 ml. Concentrations of 3·0 and 2·8 mg. per 100 ml. were found during and at the end of corticotrophin therapy respectively, and five days after the drug was stopped the level was 3·0 mg. per 100 ml.

In case 2, corticotrophin or steroid hormones were given four times.

Jaundice began to diminish within ten days after treatment had been started, although coincident improvement unrelated to therapy could not always be excluded. On the first occasion a dose of 100 units of corticotrophin daily reduced the serum-bilirubin from 14·0 to 4·8 mg. per 100 ml. in twelve days, and treatment with prednisone (40 mg. daily for one week) later reduced the serum-bilirubin from 15·7 to 6·4 mg. per 100 ml. Subsequently outpatient treatment with 50 or 100 mg. of prednisone daily has been followed by clearing of the jaundice.

In case 2, spasm of the sphincter of Oddi being thought to be a possible cause of the jaundice, therapy with atropine, pethidine, amyl nitrate, and papaverine was

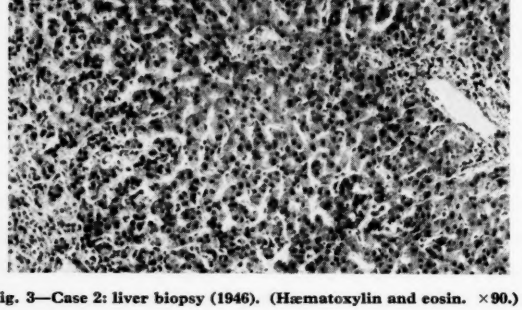

Fig. 3—Case 2: liver biopsy (1946). (Hæmatoxylin and eosin. ×90.)

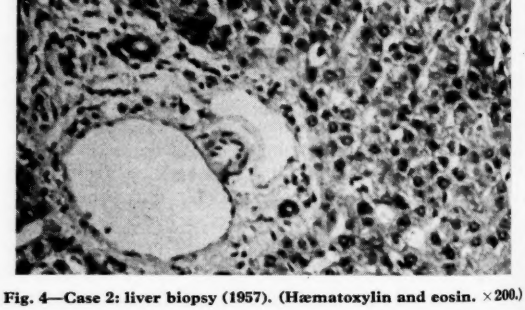

Fig. 4—Case 2: liver biopsy (1957). (Hæmatoxylin and eosin. ×200.)

tried, but none had any effect. Similarly, the instillation of saturated magnesium-sulphate solution directly into the duodenum was ineffective clinically, although an increased flow of bile followed once. Intraduodenal instillations of papaverine, arachis oil, promethazine, and sodium nitrite were also attempted, but with negative results. On two occasions a T-tube was left in the common bileduct after laparotomy, for periods of six and seven months, and the jaundice cleared. The significance of this is uncertain, especially as drainage of the common bileduct hastens recovery from intrahepatic jaundice due to hepatitis (McSwain et al. 1958) as well as from extrahepatic jaundice.

Discussion

The clinical, biochemical, and histological features in both patients are those of recurrent "obstructive" jaundice, while the radiological and surgical findings suggest that the lesion is in the liver rather than the bileducts. The sixteen-year and thirty-seven-year histories, the absence of histological evidence of chronic liver damage, and the ultimate recovery from each of the many episodes of jaundice all show that the disorder is benign—that is, provided the nutritional consequences of steatorrhœa following long-continued bile retention (Atkinson et al. 1956) are treated with parenteral fat-soluble vitamins and an adequate calorie intake.

The presence of bile in the urine and the immediate positive direct van den Bergh reaction reflect the conjugation of circulating bilirubin to water-soluble glucuronide by the liver. This differentiates the condition from the constitutional hyperbilirubinæmia described by Crigler and Najjar (1952), in which defective transferase activity is thought to impair the enzymatic conjugation of bilirubin (Schmid 1957), and from other diseases often grouped under the title of benign non-hæmolytic icterus or "Gilbert's disease". Similarly, the presence of bile in the urine, together with the more specific hæmatological investigations reported, excludes the possibility of jaundice due to increased hæmolysis.

TABLE II—COMPARISON OF DUBIN-JOHNSON JAUNDICE AND INTRAHEPATIC OBSTRUCTIVE JAUNDICE DUE TO DRUGS WITH FINDINGS IN PRESENT CASES

—	Dubin-Johnson jaundice (Dubin 1958)	Intrahepatic obstructive jaundice due to drug reactions (Gutman 1957)	Present cases
Family history	33% +	−	−
Chronic recurrent jaundice	+	−	+
Prodromal symptoms	−	Often	−
Itching, severe weight loss, and hypoprothrombinæmia	−	+	+
History of drug consumption	−	+	−
Progress to chronic liver damage	−	Rarely (?)	−
Serum-bilirubin: direct positive diazo reaction	+	+	+
Serum-bilirubin 20 mg. per 100 ml.	−	Rarely	+
Serum-alkaline-phosphatase	10% slightly elevated	Very high	High
Hypercholesterolæmia	−	+	−
Flocculation-turbidity tests	40–50% pos.	Usually neg.	Neg.
Bile in urine	+	+	4+
Liver histology	Intracellular pigment (? lipofuscin)	Bile stasis "cholangitis", and cellular infiltration (sometimes eosinophilic) in portal areas	Bile stasis and round-cell infiltration in portal areas

The cases described here are rather more difficult to distinguish from the constitutional hyperbilirubinæmia with obstructive features described by Dubin and Johnson (1954), and from intrahepatic biliary obstruction caused by drug reactions (see table II).

The length of the histories and the presence of bile in the urine are comparable with the Dubin-Johnson syndrome, but the absence of pigmentation in the hepatic cells excludes this diagnosis, as do other features in our patients—especially the degrees of hyperbilirubinæmia and the raised alkaline-phosphatase levels. Moreover, itching and metabolic complications of biliary obstruction are not reported in the Dubin-Johnson syndrome (Dubin 1958). A biochemical and histological similarity to obstructive jaundice due to drug sensitivity can also be perceived, but no accepted or apparent precipitating factor could be incriminated, and no instances of jaundice due to drugs or other sensitising agents have been recorded with recurrent episodes of jaundice from early life. Moreover, serum-cholesterol values remained normal, and eosinophilia was not present in the peripheral blood or in the liver sections.

No family history of jaundice or consanguinity was obtained in either patient, but failure to trace the father and his relative in case 1 prevents a definite conclusion in this respect. The underlying mechanism and precipitating factors for the attacks of jaundice therefore remain obscure. Although the proportions of the mono-glucuronides and di-glucuronides of bilirubin and their significance in relation to the various types of obstructive jaundice have not yet been defined, the prominence of itching in these patients suggests a defect in bile excretion rather than one of pigment metabolism.

A chemical or physicochemical disorder affecting the transport of individual components of the bile across the liver-cell membrane or in the bile canaliculi and capillaries must therefore be considered—probably one affecting those constituents, such as bile pigments and salts, which are highly concentrated by an active mechanism. The possibility of intermittent alterations in the physical characteristics of the bile itself is less likely in view of the operative findings of normal gallbladder bile in case 2. The response of the jaundice to corticotrophin and steroid drugs was variable, and it is particularly difficult to evaluate in terms of therapy or ætiological implications, as reduction in serum-bilirubin levels may occur in any type of jaundice in response to such treatment (Chalmers et al. 1956).

The evidence put forward strongly suggests that these cases represent a hitherto undescribed type of benign recurrent jaundice which should be included in the so-called "constitutional hyperbilirubinæmias". This diagnosis probably embraces several diseases with varied clinical findings and uncertain metabolic causes, but a more rational classification will probably be produced in the future. Meanwhile, current knowledge cannot exclude the necessity for one laparotomy in the diagnosis of patients such as those we have described, but the repeated hospital admissions and further operations that used to be thought necessary can probably be avoided. Outpatient treatment appears practicable in view of the ultimately good prognosis for each episode of jaundice, while special emphasis in management should be placed on the possibility of nutritional complications and the relief of itching. A trial of corticotrophin or steroid therapy is also indicated.

Summary

Two cases of an apparently hitherto unrecorded type of recurrent obstructive jaundice are described.

The disorder is characterised by recurrent attacks of jaundice and itching, each lasting months or even years,

associated with an " obstructive " pattern in the liver-function tests. No abnormality can be found during periods of remission.

The radiological and surgical findings indicate that the lesion is intrahepatic, but there are no characteristic histological changes in the liver other than those suggesting intrahepatic biliary obstruction. The prognosis for each attack is good, provided that the nutritional complications are treated.

The ætiology is unknown.

We wish to thank Dr. F. Avery Jones for permission to report case 1, and Prof. M. L. Rosenheim for permission to report case 2. We also wish to thank Dr. R. A. B. Drury and Professor Sheila Sherlock for reporting on the liver biopsy of case 1, and Sir Roy Cameron for reporting on case 2.

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EFFECT OF BILATERAL OVARIECTOMY ON CORONARY-ARTERY DISEASE AND SERUM-LIPID LEVELS

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As long ago as 1802, Heberden suggested that there was a sex difference in the incidence of angina pectoris. He wrote: " I have seen nearly 100 people under this disorder, of which number there have been three women and one boy 12 years old. All the rest were men, near, or past the fiftieth year of their age." Subsequently there have been many reports indicating that in civilised communities, with the exception of the American Negro population, the clinical manifestations of coronary atherosclerosis are commoner in men than in women.

In Britain, Mackenzie (1923) estimated that the ratio of men to women was as high as 7/1, but others (Cassidy 1946, Ryle and Russell 1949, Oliver and Boyd 1955, Peel 1955) have reported ratios between 2·4/1 and 4/1. In the United States, there have been several similar studies of patients with coronary-artery disease, and the results of four large surveys (Hedley 1939, Parker et al. 1946, Block et al. 1952, Wright et al. 1954) of more than 16,000 patients indicate a male/female ratio of 3·2/1. In Sweden also there is an overall male predominance (Biorck et al. 1957).

TABLE II—SERUM-CHOLESTEROL LEVELS IN 213 HEALTHY WOMEN

Age-group (yr.)	No.	Mean serum-cholesterol (mg. per 100 ml.)	Standard deviation
20–24	22	188	18
25–29	20	187	24
30–34	16	193	14
35–39	31	190	17
40–44	27	218	27
45–49	21	217	25
50–54	30	240	32
55–59	19	259	31
60–64	16	241	18
65–70	11	233	21

Significance of difference between means of 45–49 age-group and 50–54 age-group (t test: $0{\cdot}01 > P > 0{\cdot}001$).

Of greater interest is the observation that this male predominance of clinical coronary-artery disease is dependent on age. The greatest incidence is in the 30s and early 40s, and it decreases over the next 30 years until there is little sex difference at 70.

For example, an analysis of 1000 consecutive patients admitted to the Edinburgh Royal Infirmary for treatment of angina or myocardial infarction showed a male/female ratio which decreased from 16/1 under 40 to 1/1 over 70 (Oliver and Boyd 1955, 1958). Since the incidence of clinical coronary-artery disease in men continues to rise and reaches a peak in the late 50s, the negative correlation of the sex ratio with increasing age indicates that during the sixth decade there is a proportionately greater increase in the incidence of coronary-artery disease in women than in men. This observation is supported by an analysis of the Registrar General's statistics (1953–57). In table I the total annual deaths from " coronary disease " (International Classification no. 420.1) have been calculated as a percentage of the estimated total mid-year population in each quinquennial age-group from 40 to 69 years, and expressed as the rate per 10,000 living; although there are more male deaths from coronary-artery disease at all ages in this group, the increase in death-rate is significantly greater in women during and after the sixth decade.

There is fairly general agreement of an association, but not necessarily any causal relationship, between elevated serum-lipid levels and coronary-artery disease. It is of interest, therefore, that women over 50 have a significantly higher level of serum-cholesterol than younger women (Oliver and Boyd 1953b, 1958, Adlersberg et al. 1956, Robinson et al. 1957). In table II the mean serum-cholesterol (Sperry and Webb 1950) of apparently healthy women (mostly students and members of university and hospital teaching, technical, and domestic staff) is analysed by quinquennial age-groups. During the sixth decade there is a significant rise in the serum-cholesterol of women which is not seen in men of comparable age.

It would be interesting to know how closely the rise in clinical coronary-artery disease during and after the sixth decade and the higher cholesterol levels in women over 50 can be related to the menopause and the associated

TABLE I—THE NUMBER OF DEATHS FROM " CORONARY DISEASE " (NO. 420.1) AND THE RATE PER 10,000 LIVING EXPRESSED BY SEX AND QUINQUENNIAL AGE-GROUPS FOR THE FIVE-YEAR PERIOD 1953–57

Age-group (yr.)	Males			Females			Male/female ratio per 10,000 living
	No. of deaths from coronary-artery disease	Rate per 10,000 living (from estimated mid-year population)	Increase over 40–44 age-group	No. of deaths from coronary-artery disease	Rate per 10,000 living (from estimated mid-year population)	Increase over 40–44 age-group	
40–44	3947	4·6	..	536	0·6	..	7·6 : 1
45–49	8936	10·9	× 2·3	1409	1·7	× 2·8	6·4 : 1
50–54	16,603	22·2	× 4·7	2980	3·7	× 6·2	6·0 : 1
55–59	23,006	38·5	× 8·3	6185	8·5	× 14·2	4·5 : 1
60–64	29,776	61·3	× 13·2	11,948	18·9	× 31·5	3·2 : 1
65–69	36,623	92·5	× 19·9	20,098	37·0	× 61·6	2·5 : 1

endocrine involution. Accordingly, we undertook a study to determine whether a premature menopause is followed by a significant change in the incidence of coronary-artery disease and in cholesterol levels.

The Study

In women the maximum incidence of clinical coronary-artery disease is between 60 and 65, this peak being about 5 years after the maximum incidence in men (Hedley 1939, Master et al. 1939, Parker et al. 1946, Block et al. 1952, Wright et al. 1954, Peel 1955). Since the peak incidence in women is about 15 years after the menopause, we thought that any investigation into the effects of a premature menopause would be best confined to women who had had surgical removal of both ovaries 15 or more years before the start of the study; and, to avoid the moving population of the war years, only women operated on 20 or more years previously were studied. Further, we thought that the age of these women at the time of study should be about 10 years less than the peak incidence of coronary-artery disease. For these reasons, a survey was made of women admitted to a gynæcological unit during the 5-year period 1934–38, when they were 35 years of age or less. Thus, no woman was older than 59 at the time of study. There were 2181 such women, of whom 101 had had unilateral ovariectomy and 112 had had hysterectomy with bilateral ovariectomy. The first 100 from each group were selected for this study.

TABLE III—REASONS FOR EXCLUDING FROM STUDY WOMEN WHO HAD UNILATERAL OR BILATERAL OVARIECTOMY 20 OR MORE YEARS PREVIOUSLY

—	Unilateral ovariectomy (no. of patients)	Bilateral ovariectomy (no. of patients)
Sent for	100*	100†
Traced	39	48‡
Reasons for exclusion:		
Subsequent unilateral ovariectomy between 1939 and 1959	6	0
Thyrotoxicosis	0	1
Diabetes mellitus	1	0
Now living more than 300 miles away	1	8 (5 emigrated)
Unwilling to attend	0	3
Total excluded	8	12
Total included	31	36

* Consecutive patients between January, 1934, and December, 1938.
† Consecutive patients between January, 1934, and October, 1938.
‡ 6 patients sent for because of unilateral ovariectomy had had the other ovary removed before 1939.

The intervening war and the postwar housing programme made the study difficult, and it has been possible to trace only 87 of the 200 patients originally selected. Of these 87 patients, 67 were included in the study (66 attended for clinical examination) and 20 were rejected from the study for various reasons (table III). 5 others are known to have died during the 20 years after operation. In the unilateral ovariectomy group there were 3 deaths—2 due to rheumatic heart-disease (at 39 and 42), and 1 to cholangitis following cholecystectomy (at 54). In the bilateral ovariectomy group, the 2 deaths were due to carcinoma of the breast (at 44) and coronary thrombosis (at 41); reference is made to the latter patient later in this paper. The reasons for the gynæcological operations are listed in table IV: 2 women who had unilateral ovariectomy had a subtotal hysterectomy at the same time, and all the 36 women who had both ovaries removed had a simultaneous subtotal or total hysterectomy. After bilateral ovariectomy none of the patients had œstrogen-replacement therapy for more than 3 months. The mean age of both groups at the time of operation was 30 years.

TABLE IV—REASONS FOR GYNÆCOLOGICAL OPERATIONS 20 OR MORE YEARS PREVIOUSLY

Reason	Unilateral ovariectomy (no. of patients)	Bilateral ovariectomy (no. of patients)
Cystic ovary	13	8*
Chronic salpingitis	8	10
Tubercular salpingitis	0	6
Ectopic pregnancy	9	0
Ectopic pregnancy with salpingitis or ovarian cyst on other side	0	3
Metropathia hæmorrhagica	1	5
Fibroids	0	3
Endometrioma and double uterus	0	1
Total	31	36

* 6 patients had two separate unilateral ovariectomies.

The 66 women interviewed were seen in a general medical outpatient department, where it was explained that the object of their visit was to assess the results of their gynæcological operation. A full clinical history from the time of the operation was obtained, particular attention being given to the gynæcological aspect so as not to reveal any interest in the incidence of heart-disease. It is hoped that these women did not suspect that the inquiry was anything but a routine gynæcological survey, and for this reason the heart was not examined clinically. Two blood-pressure readings were taken from each patient when prone; the second, recorded 5 minutes after the first, is the figure given in table V. Each patient's weight was measured. A 12-lead electrocardiogram (E.C.G.) was recorded; when equivocal, an exercise-tolerance test was performed on the Master two-step mounting block. 6 ml. of blood was withdrawn; the serum-total-cholesterol was estimated by the Sperry and Webb (1950) modification of the Sperry-Schoenheimer technique, and the serum-total-lipid-phosphorus by the molybdenum-blue method of Allen (1940). The concentration of cholesterol on the α and β lipoproteins was estimated by the filterpaper-electrophoretic method of Boyd (1954).

As well as studying the two groups of women after ovariectomy, information was sought about the incidence of coronary-artery disease in a healthy population from a general practice in Edinburgh. Of the 4191 patients in this practice, there were 257 women between the ages of 45 and 59. Each of these women was interviewed by her family doctor and asked whether she had ever had exertional pain or tightness or heaviness in the chest or arms. When the answer was in the affirmative, an E.C.G. was taken wherever possible.

Results

The main clinical findings are shown in table V. During the 20 years since operation, features of coronary-artery

TABLE V—CLINICAL FEATURES OF WOMEN 20 OR MORE YEARS AFTER UNILATERAL OR BILATERAL OVARIECTOMY

Clinical features	Unilateral ovariectomy		Bilateral ovariectomy	
	No. of patients	Average duration (yr.)	No. of patients	Average duration (yr.)
Total no.	31	..	36	..
Mean age (yr.)	52	..	51	..
Age range (yr.)	42–48	..	37–58	..
Angina of effort	1	3	8	4¼
Coronary thrombosis 11 years after operation (necropsy finding)	0	..	1	..
Breathlessness on effort:				
Cardiac grade 2	8	5	15	4
Cardiac grade 3	1	3	3	1½
Diastolic blood-pressure > 100	10	?	12	?
Obesity (20 lb. in excess of standard weight)	4	12	3	14

disease developed in 9 of 36 women who had had bilateral ovariectomy, and in 1 of 31 who had had unilateral ovariectomy.

The diagnosis of coronary-artery disease was made primarily on the patient's description of angina pectoris. Where this seemed equivocal, the patient was regarded as not having angina; there were 2 such patients, 1 in the bilateral-ovariectomy group and 1 in the unilateral-ovariectomy group.

Secondary supportive evidence for the diagnosis of coronary-artery disease was obtained from necropsy in one patient, and from E.C.G.s in the majority of the other patients (table VI). There is general agreement that myocardial ischæmia can cause ST/T-wave changes after exercise, left bundle-branch block, and the ST depression and asymmetrically inverted T wave of "left ventricular strain". The E.C.G. findings in those women without clinical features of coronary-artery disease are shown in tabel VII.

TABLE VI—E.C.G. FINDINGS IN PATIENTS WITH CLINICAL EVIDENCE OF CORONARY-ARTERY DISEASE

Description of study	Age (yr.)	E.C.G. findings	
		At rest	After exercise test
Bilateral ovariectomy	41	No E.C.G. but evidence of coronary thrombosis at necropsy	Not done
	49	Normal	Negative
	49	Old posterior myocardial infarct	Not done
	51	ST/T-wave abnormalities	Positive
	52	Complete left bundle-branch block	Not done
	52	Left ventricular hypertrophy and "strain"	" "
	53	Normal	Negative
	55	ST/T-wave abnormalities	Positive
	56	Left ventricular hypertrophy and "strain"	Negative
Unilateral ovariectomy	47	Left ventricular "strain"	Positive
General-practice group	50	Normal	Negative
	50	Old anteroseptal infarct	Not done
	53	ST/T-wave abnormalities	Negative
	53	Normal	"
	54	Normal	"
	57	Old anterior infarct	Not done
	57	ST/T-wave abnormalities	Positive
	57	Normal	Negative
	58	Left ventricular hypertrophy and "strain"	Not done

1 woman in the bilateral-ovariectomy group died from myocardial infarction before this study was started.

She was 41 years old, and, according to her husband, was healthy until 11 years after the operation when she went with him to a dance. After dancing for about an hour and a half, she suddenly slumped away from her partner and fell on to the floor dead. Necropsy revealed a fresh fleshy thrombus, not organised and 2 cm. long, in the anterior descending branch of the left coronary artery, 1 cm. below its origin. There was no evidence of recent myocardial infarction. The left coronary artery and its anterior descending branch both showed extensive coronary atheroma, and the circumflex branch was occluded by atheroma soon after its origin. There was myocardial fibrosis in the high anterolateral region of the left ventricle.

TABLE VII—E.C.G. FINDINGS IN PATIENTS WHO HAD NO CLINICAL EVIDENCE OF CORONARY-ARTERY DISEASE

E.C.G. findings	Unilateral ovariectomy	Bilateral ovariectomy
Normal resting E.C.G.	25	19
Minor flattening of T-waves at rest, with normal exercise test	1	3
Left ventricular hypertrophy	2	0
ST/T-wave changes of left ventricular "strain"	2	2
Long PR interval (0·28 sec.)	0	1
Complete right bundle-branch block	0	1
Multiple ventricular extrasystoles	0	1

TABLE VIII—MEAN WEIGHT (LB.) AT AND AFTER UNILATERAL AND BILATERAL OVARIECTOMY

Time	Unilateral ovariectomy (31 women)	Bilateral ovariectomy (35 women)
Operation	110	107
5 years later*	117	134
10 years later*	119	142
At time of examination	141	139

* Verbal evidence only.

More patients were significantly breathless on exertion in the bilateral-ovariectomy group than in the other group. There was no difference in the prevalence of diastolic hypertension or obesity between the two groups.

When examined, the mean weight of the women who had had unilateral ovariectomy was 141 lb., and of those who had had both ovaries removed 139 lb. Although there was no significant difference in these mean weights, there was a difference 5 and 10 years after operation (table VIII). The figures at the time of operation and examination were measured in hospital, whereas the intermediate figures were from the patients' memory and may be less accurate.

Nevertheless, the majority of women had experienced an abrupt increase in weight within 2 years of bilateral ovariectomy, whereas the majority who had had only one ovary removed did not notice any obvious weight increase until the menopause.

Table IX supports the view that women who had had unilateral ovariectomy were representative of the healthy population, and therefore provided a satisfactory control group. The incidence of clinical coronary-artery disease in this group compares closely with that in 257 healthy women between the ages of 45 and 59 interviewed in a general practice in Edinburgh, and also with the incidence in the Framingham study (Dawber et al. 1957). The difference in the incidence of clinical coronary-artery disease between the bilateral-ovariectomy and unilateral-ovariectomy groups is statistically significant (χ_c=4·62: 0·02 > P > 0·01).

The measurements of serum-cholesterol and the cholesterol/phospholipid (C/P) ratio are shown in table X. There is elevation of these values in the bilateral ovariectomy group compared with the unilateral ovariectomy group, and this difference is statistically significant (for total cholesterol $P < 0.01$: for C/P ratio $P < 0.001$). α/β lipoprotein ratios were determined in 12 women in each group: 12% of the serum-total-cholesterol was attached to the β-lipoprotein fraction in the bilateral group, and 21% in the unilateral group. This difference is significant at the 0·02 level. Among the women from whom both ovaries had been removed, the serum-lipid levels of those who had developed features of coronary-artery disease were not significantly different from those who appeared healthy.

These findings indicate that both clinical coronary-artery disease and elevated serum-cholesterol levels are commoner in women who have had both ovaries removed

TABLE IX—INCIDENCE OF CORONARY-ARTERY DISEASE IN OVARIECTOMY GROUPS AND OTHER STUDIES

Description of study	Total no. of women	Age range (yr.)	No. with coronary-artery disease	%
Bilateral ovariectomy	36	37–58	9	25·0
Unilateral ovariectomy	31	42–58	1	3·2
Edinburgh general practice	237	45–59	9	3·5
Framingham study	1502	40–59	24	1·8

prematurely than in those who have had only one ovary removed. Additional evidence is shown in table XI, which refers briefly to 8 castrated women seen because of ischæmic symptoms in the department of cardiology of the Edinburgh Royal Infirmary during the past six years.

Discussion

This study suggests that the surgical removal of both ovaries from premenopausal women is followed by the premature development of clinical features of coronary-artery disease. In contrast, the surgical removal of one ovary from women of comparable age did not influence the incidence of coronary-artery disease twenty years later. Furthermore, after bilateral ovariectomy the serumlipid levels were higher than after unilateral ovariectomy.

These observations give some factual support to the suggestion that in women the rise in the incidence of clinical coronary-artery disease during and after the sixth decade, and the increase in serum-cholesterol after the age of 50, may both be due to menopausal ovarian involution. These changes are unlikely to be caused by any fundamental difference in the diet of postmenopausal women. Studies of the food consumption of middle-aged and elderly women suggest that with advancing age the total calorie and fat intakes decrease slightly (Widdowson and McCance 1936, Baines and Hollingsworth 1955, Sinclair 1956).

TABLE X—SERUM-TOTAL-CHOLESTEROL AND THE SERUM-TOTAL-CHOLESTEROL/PHOSPHOLIPID RATIO AFTER UNILATERAL OR BILATERAL OVARIECTOMY 20 OR MORE YEARS EARLIER

—	Unilateral ovariectomy	Bilateral ovariectomy	Significance (t test)
No. of patients	31	35	..
Mean serum-cholesterol (mg. per 100 ml.)	217±56	251±43	$0{\cdot}01 > P > 0{\cdot}001$
Mean C/P ratio	0·76±0·11	0·94±0·10	$P < 0{\cdot}001$

Although the difference between the two groups studied can probably be related to the complete removal of ovarian hormones consequent upon bilateral ovariectomy, this should be qualified by stating that a subtotal or a total hysterectomy was performed in all the women from whom both ovaries were removed but in only 2 from whom one ovary was removed. To assess the significance of this variable, an investigation should have been made of a comparable group of young women who had had hysterectomy only; unfortunately, this was not possible because isolated hysterectomy is very uncommon in women aged 35 or less and was performed in only 14 of the 2181 women under survey. The possibility that hysterectomy was responsible for the observed differences must be taken into account, though there is much evidence relating ovarian function to the incidence and development of coronary-artery disease and to changes in the circulating lipids, and none indicating that the presence of a uterus is important. This difference between the two groups of women seems unlikely, therefore, to be pertinent.

The results of this investigation can be related to the findings in other studies.

In the Mayo Clinic, Wuest et al. (1953) studied at necropsy the hearts of 49 women in whom bilateral ovariectomy had been performed several years earlier, and found that the degree of coronary atheroma was greater when compared by decade with women in whom both ovaries were intact. This difference was not apparent, however, unless the ovaries had been removed at least 5 years before necropsy. Rivin and Dimitroff (1954) made similar observations and agreed with the earlier authors that in women after bilateral ovariectomy the incidence of coronary atheroma approaches that of men.

Robinson et al. (1957) suggested that the serum-lipids increase after bilateral ovariectomy, but unfortunately most of their patients had associated overt coronary-artery disease, and it is not clear whether the lipid levels of women without associated coronary-artery disease were significantly different from those of normal women of the same age. Recently Robinson (1959) has stated that further studies suggest a significant elevation of serum-cholesterol after bilateral ovariectomy. Complementary to these observations after bilateral ovariectomy are the necropsy findings of Hawke (1950), who reported less coronary atheroma in eunuchs than in normal men. Moreover, Furman and Howard (1957) showed that in eunuchs the plasma-cholesterol level and C/P ratio are lower, and the concentration of high-density (α) lipoproteins is greater, than in non-castrated men.

Thus, these various studies of the effect of removing the gonads on the incidence of the clinical features of coronary-artery disease, on the serum-lipid levels and on the development of coronary atheroma agree well, and they imply that the removal of functioning ovaries can lead to premature development of coronary-artery disease. Moreover, coronary-artery disease is uncommon in women with normally functioning ovaries, and it is appropriate to reiterate Cassidy's (1946) comment that not only may masculinity predispose to coronary-artery disease but femininity may also safeguard against it. Although in the future new ovarian steroids may be isolated, it has been suggested that endogenous œstrogens are partly responsible for this low incidence of coronary-artery disease in premenopausal women (Oliver and Boyd 1953a).

In support of this, we have observed regular cyclical depression of the serum-cholesterol and β-lipoprotein cholesterol at the midpoint of the menstrual cycle of healthy young women (Oliver and Boyd 1953a, 1955); and the endogenous secretion of œstrogens is believed to be maximal at this point in the cycle (Smith and Smith 1936, Brown 1955, 1957). Several workers (Barr et al. 1952, Barr 1953, Oliver and Boyd 1954, 1956, Steiner et al. 1955) have confirmed and elaborated Eilert's observation (1949, 1953), and agree that the administration of œstrogens decreases the serum-cholesterol and β-lipoprotein cholesterol and increases the serum-phospholipids and α-lipoprotein cholesterol. Progesterone, on the other hand, does not affect significantly the circulating lipids in man (Oliver and Boyd 1956).

TABLE XI—SOME OBSERVATIONS ON 8 ADDITIONAL WOMEN WHO PRESENTED WITH ISCHÆMIC SYMPTOMS AND HAD BILATERAL OVARIECTOMY UNDER THE AGE OF 40

Age when first seen (yr.)	Age at bilateral ovariectomy (yr.)	Duration of angina (yr.)	E.C.G.	Blood-pressure (mm. Hg)	Serum-cholesterol (mg. per 100 ml.)	C/P ratio	α/β lipoprotein ratio
30	27	0	Anteroseptal infarct	182/112	495	1·10	6/94
37	22	2	Myocardial ischæmia after exercise	138/86	288	0·96	12/88
39	31	2	Myocardial ischæmia after exercise	114/78	252	0·87	13/87
42	39	1	Myocardial ischæmia at rest	155/100	250	0·87	12/88
42	39	0	Anteroseptal infarct	135/65	290	1·05	9/91
49	29	3	Myocardial ischæmia at rest	160/95	251	0·90	14/86
49	38	9	Anterior infarct	170/100	577	1·56	9/91
49	38	3	Myocardial ischæmia at rest	186/108	324	0·94	10/90

The mechanism of this action of œstrogens is complex and unresolved (Boyd and Oliver 1958). Although large doses of œstrogens increased the level of serum-precipitable iodine (Engstrom and Markardt 1954), bilateral ovariectomy in premenopausal women did not affect thyroid function (Stoddard et al. 1957). Endogenous œstrogen secretion decreases after bilateral ovariectomy in premenopausal and postmenopausal women. Bulbrook and Greenwood (1957) and Bulbrook et al. (1958) have shown that bilateral ovariectomy in premenopausal women is followed by marked and permanent reduction of urinary œstrogen excretion. Bulbrook and Greenwood (1957), Marmorston et al. (1957), and McBride (1957) report that urinary œstrogen excretion decreases in postmenopausal women gradually over at least 20 years; it correlates with the gradual postmenopausal increase in the incidence of coronary-artery disease, and suggests an inverse relationship. Furthermore, both men and postmenopausal women show a significant decrease in urinary œstrogen excretion after myocardial infarction (Marmorston et al. 1955, Bauld et al. 1956, Bersohn and Oelofse 1958). It is reasonable, therefore, to conclude that bilateral ovariectomy and a normal menopause are both followed by an increase in the incidence of coronary-artery disease, and by elevated serum-lipid levels, as a result of decreased endogenous œstrogen secretion.

The results of this study indicate two practical conclusions. Wherever possible complete removal of both ovaries should be avoided in premenopausal women, but when this operation must be done or the ovaries have to be irradiated œstrogen replacement therapy should be given until about the age of 50. This should be the rule rather than the exception—indeed, probably the only exceptions are women in whom it is desirable to reduce endogenous œstrogen secretion for treatment of breast cancer. A case could even be made out for administering small doses of œstrogens for a number of years to all menopausal women.

Summary

In women, the incidence of clinical manifestations of coronary-artery disease rises rapidly during and after the sixth decade. Serum-lipid levels also rise significantly after the age of 50.

Two groups of women who had either one or both ovaries removed 20 or more years previously when aged 35 or less were studied. Bilateral ovariectomy was followed by the premature development of clinical coronary-artery disease and significant elevation of the serum-lipid levels.

Ovarian œstrogen secretion seems to be inversely related to the development of coronary-artery disease and to elevated serum-lipid levels.

Œstrogen-replacement therapy should probably always be given to women under 50 years of age who, for gynæcological reasons, have had both ovaries removed or irradiated.

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CANCER IN ULCERATIVE COLITIS

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DESPITE earlier doubts concerning the association of carcinoma of the large bowel and ulcerative colitis, numerous series published in the past fifteen years indicate a definite association. In 9469 patients with ulcerative colitis seen at hospital, 358 cases of carcinoma have been reported (table I), an overall incidence of 3·8%; in 871 cases from the Mayo Clinic a comparable incidence (3·2%) was observed in adults, while 6·3% of 28 affected children under the age of 16 also had carcinoma (Jackman et al. 1940). Despite varying periods of follow-up, these figures represent a higher incidence than in the general population; death from cancer was found by Bargen et al. (1954) to be thirty times commoner in 1564 cases of ulcerative colitis than in the general population of the same age and sex. Weckesser and Chinn (1953) placed the colon-cancer rate in the normal population at 0·06% and also found it to be increased thirtyfold to 1·9% (95 in 4806 cases) in those with ulcerative colitis. Deaths due to cancer in a similar comparison (Goldgraber et al. 1958a)

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show a ninefold increase for the colon and fourfold for the rectum.

In the past decade the development of surgery in the treatment of ulcerative colitis has brought increasing awareness of the serious problem of carcinomatous change; moreover the incidence of this complication in purely surgical series is often two to three times that in medical. Cattell (1948) reported a general incidence of 7%, rising to 1 in 3 in those who had had ulcerative colitis for nine years or more, compared with 3·9% (9 cases in 226), rising to 36% in those with colitis for longer than twelve years in the series of Lyons and Garlock (1951). A similar proneness to carcinoma in the longstanding case has been observed by others (Counsell and Dukes 1952, Dennis and Karlson 1952, Wheelock and Warren 1955, Bacon et al. 1956).

We report here a further 18 cases of malignant change in ulcerative colitis and try to assess both the prognosis of this complication and factors that may influence it. The case-records are summarised in table II; 15 of the 18 cases were part of a series of 222 cases of ulcerative colitis referred for surgery, an incidence of 6·7%; but of the patients who had ulcerative colitis for ten years or more, 17% developed carcinoma; the 3 remaining cases are reported by courtesy of other surgeons. Of the 18 patients, 7 are already dead and only 3 have so far survived for five years or longer.

Survival

As far as can be ascertained, some 450 cases of carcinoma complicating ulcerative colitis have been reported, but only 286 have been described in detail (table III); together with the present series 304 cases are therefore available for study.

Of the 304 patients, 221 died before five years and only 13 (4·2%) have so far survived five years or longer after operation; of these 13 five-year survivors, 2 have since died from carcinoma arising in a segment of colon remaining after operation, and 1 other has subsequently died of colonic metastases. Of the 70 other survivors, 7 have inoperable lesions or metastases; the remaining potential five-year survivors thus number 63.

TABLE I—REPORTED INCIDENCE OF CARCINOMA IN ULCERATIVE COLITIS

Series		Ulcerative colitis			Carcinoma		
Author	Year	No. of cases	Av. age (yr.) at onset	Duration (yr.)	Av. age at onset	No. of cases	Proportion (%) of all cases
Lynn	1945	1467	..	..	..	28	1·9
Ricketts and Palmer	1946	206	..	..	..	3	1·4
Cattell and Boehme	1947	450	27·6	9	36·6	10	2·2
Johnson and Orr	1948	164	22·5	16·5	39	2	1·2
Hayes	1949	451	33	7·3	40·3	3	0·7
Kasich et al.	1949	143	31·3	11·7	43	7	4·9
Warren and Sommers	1949	180	..	..	41	9	5·0
Strömbeck	1949	54	..	..	..	1	1·8
Lagercrantz	1949	134	..	..	..	1	0·7
Rice-Oxley and Truelove	1950	129	30	7	37	4	3·1
Glecker and Brown	1950	316	28·3	16	44·3	12	3·8
Lyons and Garlock	1951	226	20·2	19	39·2	9	3·9
Kiefer et al.	1951	226	..	..	..	10	4·4
Counsell and Dukes	1952	63	..	..	..	7	11·1
	..	..	31·4	18·3	49·7	13*	..
Dennis and Karlson	1952	267	..	..	..	12	4·5
Shands et al.	1952	..	26·7	15·3	42	73	..
Weckesser and Chinn	1953	118	19·7	10·3	30	4	3·4
MacDougall	1954	126	23·4	19·6	43	5	3·9
Bargen et al.	1954	1564	..	..	..	98	6·3
Wheelock and Warren	1955	483	..	..	..	31	6·2
Bacon et al.	1956	84	..	..	..	12	14·2†
	..	402	..	..	..	12	2·9‡
Thorlakson	1956	182	33·6	15	48·6	12	6·6
Colcock and Mathiesen	1956	307	..	..	..	11	3·6
Maltby et al.	1956	205	..	..	..	5	2·4
Dukes and Lockhart-Mummery	1957	153	..	..	..	8	5·2
Svartz and Gillnäs	1958	439	..	..	..	17	3·9
Goldgraber et al.	1958b	792	..	..	..	22	2·7
Present series	1959	222	..	..	..	15	6·7
Total		9469				358	3·8

* Includes 6 additional cases.
† Incidence in cases treated surgically.
‡ Overall incidence.

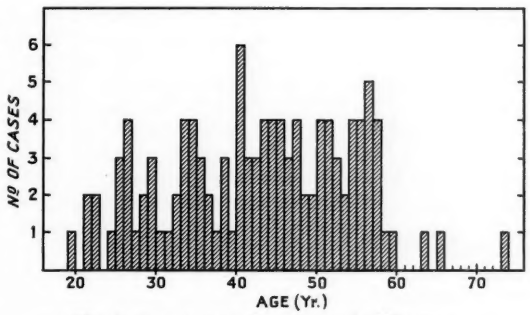

Fig. 1—Age at onset of carcinoma in 112 cases.

In the group of 304 cases, 112 are reported in sufficient detail to enable the five-year-survival rate to be calculated from the successive annual survival-rates (table IV). This is 18·6%, which means that of the whole group of 304 patients 56 might survive to five years. 13 cases have already done so; thus of the remaining 63 potential five-year survivors apparently a further 20 will die before this time. Further deaths will doubtless ensue after five years; and 18·6% probably represents a maximum, for of the 13 patients who survived for five years, 3 have subsequently died. Improvement may occur in years to come, but on this basis carcinoma complicating ulcerative colitis appears almost incurable; but unlike most carcinomas it is preventable.

Age at Onset and Duration of Disease

Commonly ulcerative colitis begins in the third decade of life and carcinoma supervenes early in the fifth; in the cases under review (table I) the average age at onset of the disease was 27·3 years with subsequent development of carcinoma at 41·1 years after the patients had had ulcerative colitis for an average of 13·9 years. The various series comprising this total differed widely; but sufficient evidence for statistical analysis can be obtained from twelve series (including our own) thus providing 112 cases. Every case from these series has been included without selection. There is no significant difference between the samples regarding age of onset of ulcerative colitis, though there is a slight difference in the relationship between age of onset of carcinoma and duration of disease; possibly this reflects the varying duration of follow-up since the longer a group is followed the more likely are new cases of cancer to develop.

In these 112 cases the average age of onset of ulcerative colitis was 27·7 years with subsequent development of carcinoma at 42·5 years after ulcerative colitis had been present for an average of 14·8 years. These figures are comparable with those given above for the whole group. The common age for the development of cancer of the large intestine in patients with previously normal bowel is above 42 years. In 1954, 710 cases of carcinoma of the colon and rectum were treated in the hospitals of the Birmingham area; the average age of the patients with carcinoma of the colon was 63·2 years and with carcinoma of the rectum 64·4 years—an overall average of 63·8 years. The age range for the development of carcinoma in the 112 analysed cases is shown in fig. 1, which shows that a

considerable proportion of cases of carcinoma developed at 20–40 years of age. Of these 112 patients, 68·7% had ulcerative colitis for ten years or more before carcinoma developed; nevertheless 11·6% had the disease for only five years or less before development of neoplastic change, and 19·6% for five to ten years; thus of these 112 patients, a third had the disease for less than ten years. In our cases carcinoma was discovered at proctocolectomy five years after the onset of ulcerative colitis and 4 years after ileostomy in a patient (case 5, table III) who died six and a half years after the beginning of her illness; 2 further patients died eight years, and a 4th seven years, after the first attack of colitis.

Because malignant change is more likely to supervene in a longstanding case it must not be thought unlikely to occur in the individual case with ulcerative colitis of less than ten years' duration.

Diagnostic Difficulties

Carcinoma may remain undiagnosed until a late stage. Neoplastic change not infrequently follows a quiescent period associated with a healing phase; symptoms are then attributed to a relapse. Svartz and Gillnäs (1958) studied 17 cases of carcinoma supervening on ulcerative colitis and

TABLE III—SUBSEQUENT SURVIVAL AFTER DEVELOPMENT OF CARCINOMA

Series		Carcinoma		Dead	Five-year survivors to date
Author	Year	Incidence (%)	No. of cases		
Cattell and Boehme ..	1947	2·2	10	7	1
Johnson and Orr ..	1948	1·2	2	1	0
Hayes	1949	0·7	3	3	0
Kasich et al.	1949	4·9	7	7	0
Lahey	1949	..	17	15	0
Glecker and Brown ..	1950	3·8	12	6	0
Lyons and Garlock ..	1951	3·9	9	8	1
Counsell and Dukes..	1952	..	13	9	1
Dennis and Karlson ..	1952	4·5	12	8	0
Shands et al.	1952	..	73	57	2
Weckesser and Chinn	1953	3·4	4	4	0
MacDougall	1954	3·9	5	4	0
Wheelock and Warren	1955	6·2	31	24	2
Bacon et al.	1956	14·2	11	7	1
Thorlakson	1956	6·6	9	2	0
Maltby et al.	1956	2·4	5	5	0
Kellock and White ..	1957	..	4	2	N.S.
Svartz and Gillnäs ..	1958	3·9	17	15	N.S.
Jackson et al... ..	1958	..	1	1	0
Goldgraber et al. ..	1958b	2·7	22	14	1
Hickey and Tidrick ..	1958	6·0	19	15	1
Present series ..	1959	6·7	18	7	3
Total			304	221 (72·7%)	13 (4·2%)

N.S. = not stated.

Of the 13 five-year survivors, 3 have since died of colonic carcinomatosi

TABLE II—CARCINOMA ARISING SUBSEQUENTLY TO ULCERATIVE COLITIS

Case no.	Sex	Age (yr.) at onset of colitis	Duration of disease (yr.)	Age (yr.) at onset of carcinoma	Previous operations	Site of carcinoma	Treatment	—	Result
1	F	30	14	44	Transverse colostomy, abdominoperineal excision	Rectosigmoid	Colectomy and ileostomy 8 months later	U	No sign of metastases at 2nd operation; remains well at 1 yr.
2	M	46	8	54	..	Rectum	Carcinomatosis; inoperable	D	Died 9 days post-laparotomy
3	F	31	24	55	..	Sigmoid	Ileostomy and proctocolectomy	U	Died carcinomatosis 1 year postoperatively
4	F	36	8	44	..	Rectum	Inoperable	D	Died 10 days after admission
5	F	37	12	49	..	Rectosigmoid, splenic flexure	Proctocolectomy and ileostomy	D	Postoperative collapse and death; no metastases at necropsy
6	M	27	7	34	..	Descending colon	Laparotomy; inoperable	D	Died 10th postoperative day
7	M	24	16	40	..	Hepatic flexure	Ileostomy and proctocolectomy	U	Alive and well at 1 year
8	F	30	20	50	..	Ascending colon, hepatic and splenic flexures	Colectomy and ileostomy; A.P. excision two months later	D	Alive and well at 1 year
9	M	27	14	41	..	Transverse colon	Proctocolectomy	U	Alive and well at 1 year
10	F	34	11	45	..	Ascending colon	Colectomy and ileostomy; A.P. excision two months later	S	Alive and well at 6 years
11	F	51	4½	56	Ileostomy elsewhere 4 years previously	Rectum	Proctocolectomy	S	Died; recurrence and metastases 18 months postoperatively
12	F	30	13	43	Ileostomy 3 years previously	Rectum	Proctocolectomy	U	Alive and well at 8 years
13	F	27	30	57	Appendicostomy 26 years previously	Sigmoid	Proctocolectomy	S	Alive and well at six months
14	M	27	12	39	..	Unknown	Laparotomy; carcinomatosis peritonii	U	Died 3 months postoperatively; no necropsy
15	M	20	20	40	..	Sigmoid	Proctocolectomy after initial colostomy for abscess	U	Alive at 6 months
16	M	24	14	38	..	Sigmoid	Decompression colostomy; later colectomy	U	Immediately postoperatively alive and well
17	M	24	17	41	..	Rectum	Proctocolectomy	D	Alive and well at 5½ years
18	F	53	10	63	..	Rectosigmoid, sigmoid	Colostomy	D	Diffuse metastases in liver; remains alive immediately postoperatively

A.P. = abdominoperineal. U = undiagnosed preoperatively. S = suspected preoperatively. D = diagnosed preoperatively.

TABLE IV—SURVIVAL-RATES IN 112 PATIENTS (ACTUARIAL METHOD)

—	Time since operation (yr.)					
	Less than 1	Less than 2	Less than 3	Less than 4	Less than 5	5 or more
112 cases:						
Dead	53	14	5	4	1	3
Alive	8*	7*	4*	4	3	6
Annual survival-rate ..	$\frac{51}{104}$=49%	$\frac{30}{44}$=68·2%	$\frac{21}{26}$=80·7%	$\frac{13}{17}$=76·5%	$\frac{9}{10}$=90%	..

* Includes 1 patient alive with metastases or recurrence.

Calculated expected survival-rate if every case followed to five years = $\left(\frac{51}{104}\times\frac{30}{44}\times\frac{21}{26}\times\frac{13}{17}\times\frac{9}{10}\right)\times 100 = 18{\cdot}6\%$

found that all patients except 2 had been working regularly for two or more years before the development of carcinoma; 4 patients had been symptom-free for eight years or more. The bowel in this type of case showed within 20 cm. of the tumour a healing pattern with lymphocytic infiltration, fibrosis, and connective tissue overgrowth—a misleading pattern when reliance is placed on rectal biopsy. In a more recent series from the same hospital by Rosenqvist et al. (1959), 19 of 26 patients had a quiescent period for a year or more; moreover, these workers observe that cancer can appear in a bowel showing in addition radiological improvement. This pattern has been seen in our cases though we have also seen carcinomatous change accompanying the florid stage of the disease (figs. 2–4); the difficulties are then further increased, for the symptoms due to the carcinoma are usually identical with those due to the colitis, so there is no change in the clinical picture to give warning until pain develops—a late symptom due to pericolic or perirectal infiltration.

Fig. 2—Healing phase: atypical crypts; multilayer epithelium.

Shands et al. (1952) noted pain as the most common premonitory symptom in 87% of their patients, followed by loss of weight, increased number of stools, weakness, and anæmia, in that order of frequency. They likewise observed histologically healed or healing ulcerative colitis with secondary mucosal hyperplasia in association with carcinoma, which was multicentric in half their cases. Clinical quiescence is therefore no guarantee that carcinoma will not develop subsequently, though it may mislead in this respect as it did in case 2 (table II). Two years before his final admission, when he died of carcinomatosis, the idea of operation had been discarded on the grounds that the disease had become quiescent and that, since it had not persisted for as long as ten years, malignant change was unlikely as yet to take place.

Radiological detection of the neoplasm may be correspondingly difficult: Goldgraber et al. (1958b) report failure to demonstrate a growth in 42% of their cases—a failure rate over three times greater than in cases of carcinoma in previously healthy bowel. In numerous reported cases the presence of a carcinoma remained unsuspected before operation; this occurred in 6 of our patients. It might be thought that circumstances favour this type of case, since the lesion was discovered before it had become manifest symptomatically; of these 6 patients 1 is surviving after eight years, and 3 between one and two years after operation; but 2 are already dead.

Even at operation the growth may not be detected; this occured in 3 of our 18 cases. Subsequent detection by naked-eye inspection of the specimen may likewise be difficult (Dukes and Lockhart-Mummery 1957). Goldgraber et al. (1958b) found the mucosa to be smooth, without ulcers and with no obvious evidence of malignancy, in 5 cases shown histologically to have cancer. It seems possible therefore that deaths attributed to ulcerative colitis alone may sometimes be due to undetected cancer.

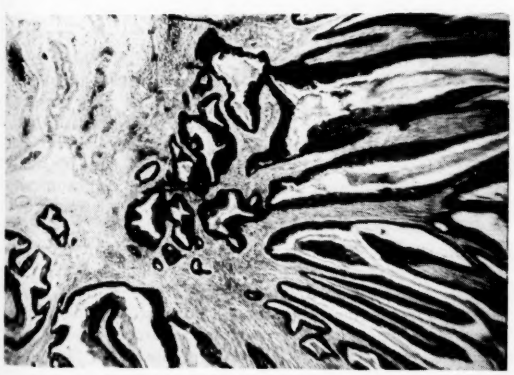

Fig. 3—Bowel a few cm. from the area in fig. 2: invasive papillary adenocarcinoma.

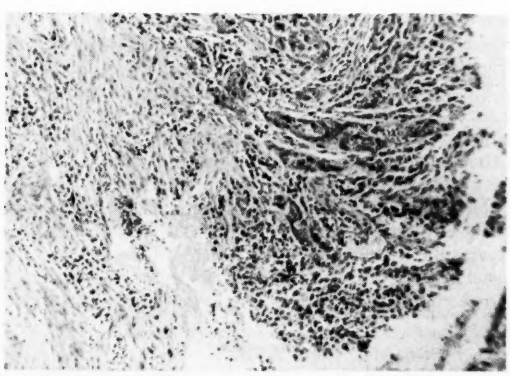

Fig. 4—Adenocarcinoma developing in the florid stage of chronic ulcerative colitis.

Cancer in "Defunctioned" Bowel

Rest in the physiological sense offers no protection against the subsequent development of cancer. The 304 reported cases of carcinoma complicating ulcerative colitis included 34 in which ileostomy, or occasionally cæcostomy or appendicostomy, had been performed some years earlier. Of these 34 cases, 17 (50%) were dead at the time of report, 2 were alive with metastases, 4 were alive without recurrence following excision at one to four years, and only 2 (8%) had survived for five years or longer. In 11 further patients carcinoma arose in the rectal stump after ileostomy and subtotal colectomy—a fact less surprising when it is realised that active ulceration can persist in the rectum for many years after ileostomy and subtotal colectomy (fig. 5). In 3 further cases, rectal carcinoma developed after ileoproctostomy (Cattell and Boehme 1947, Dennis and Karlson 1952). Lyons and Garlock (1951) have reported that of 16 cases of ulcerative colitis involving the rectum for twelve years or more, as many as 7 developed carcinoma. Since the rectum is involved in 95% of cases of ulcerative colitis, these facts provide strong indication for excision of the large bowel in toto in those who come to operation, and unlike Rosenqvist et al. (1959) we find that sexual impairment rarely follows rectal excision (we are aware of only 1 such case in many after excision for ulcerative colitis).

Fig. 5—Active disease in rectal stump ten years after colectomy and ileostomy.

Conclusion

The prognosis when cancer is fully developed is so poor—at the best 18·6% five-year survival—and methods of detection are so defective that the condition can be treated effectively only by prevention. Theoretically the cancer could always be averted since extirpation of large bowel removes the potentiality. Most surgeons would, however, shrink from recommending excision of the large bowel in all cases of ulcerative colitis, and especially in those with little disability; yet cancer develops even in these. Conventional methods of follow-up even with radiological checks are ineffective since by the time a lesion is thus detected it is usually too late for cure. The possibility of malignant change thus poses the most difficult problem in the management of patients with ulcerative colitis. It can be said, however, that where permanent irreversible changes have occurred in the mucosa, the bowel is better out, and that when for other reasons surgery is undertaken the whole of the large intestine should be removed.

Summary

From reported cases, cancer of the large intestine seems to be very much commoner in ulcerative colitis than in previously healthy patients; the incidence in medical series is between 3% and 4%, twice as high in surgical series, and 30% when ulcerative colitis has been present for ten years or more. In a personal series of 222 surgical cases the overall incidence has been 6·7%, rising to 17% in those with ulcerative colitis of ten or more years' duration.

An analysis of this series together with others suggests that the five-year-survival rate in cases of carcinoma complicating ulcerative colitis is no higher than 18·6%.

The average age at which carcinoma develops is 42 years in ulcerative colitis, compared with 63 years in previously healthy people.

Carcinoma may develop after a quiescent or healing phase. The lesion can be difficult to detect clinically, radiologically, and on naked-eye inspection of the bowel after removal.

Simple deflection of the fæcal stream by ileostomy does not protect the bowel from malignant change, which can arise both in retained and in defunctioned large intestine and in a functioning rectum after ileoproctostomy.

We acknowledge the assistance of Dr. J. Waterhouse, of the Department of Medical Statistics, for his helpful advice and criticism; and we thank Mr. Arnold Gourevitch, F.R.C.S., and Mr. Peter Bevan, F.R.C.S., for permission to refer to cases under their care.

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"... With rare exceptions, men of science feel it a social duty to communicate any new discoveries and conclusions to their professional colleagues ... so that they may participate in whatever advantages may accrue from the advance in knowledge. ... This laudable attitude is hardly ever pure; mostly it is complicated by others ... These secondary motives are naturally stimulated if the reception of the communications is a hostile one. One may be altruistically disappointed at the potential benefits of the new work being wasted, or personally chagrined at the rebuff to one's intelligence. Commonly this leads to redoubled efforts to present the conclusions in a more persuasive fashion, to counter the criticisms brought forward, and there begins the slippery slope through argumentation to controversy and finally to personal abuse. The two main disadvantages of yielding to these temptations are the waste of emotion involved and the distraction of activity from fruitful work into directions that are always futile."—ERNEST JONES, *Free Associations*; p. 208 (London: Hogarth Press).

NEW TREMOR SYNDROMES OCCURRING SPORADICALLY IN NATIVES OF THE WABAG-LAIAGAM-KUNDEP REGION OF THE WESTERN HIGHLANDS OF AUSTRALIAN NEW GUINEA

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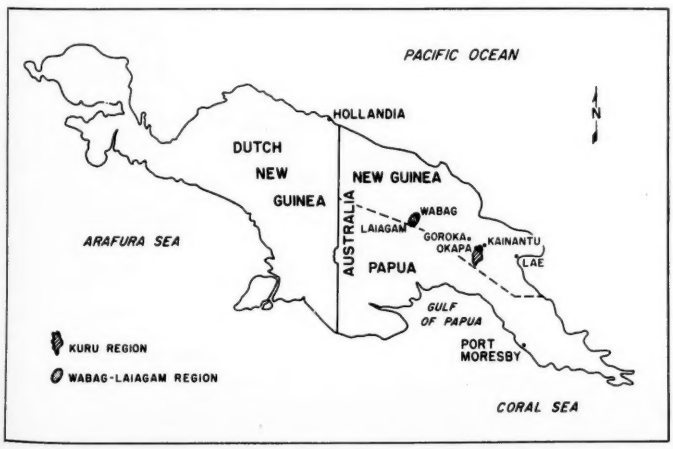
WHILE searching for kuru (Bennett et al. 1958, Curtain et al. 1959, Fowler and Robertson 1959, Gajdusek 1958, Gajdusek and Zigas 1957, 1958, 1959a, 1959b, Klatzo et al. 1959a, 1959b, Simpson et al. 1959, Zigas and Gajdusek 1957, 1959) or similar neurological disorders in new areas throughout Melanesia, we were told about a series of peculiar disturbances of the central nervous system involving tremors, some of them, kuru-like, in Enga-speaking natives of the Wabag-Laiagam-Kundep region of the Western Highlands of Australian New Guinea. So far we have seen 24 cases with tremor syndromes, but there is no indication that their incidence is anywhere as high as that of kuru in its Okapa-centred focus in the Eastern Highlands, some 170 miles away. Nevertheless in 3 of our cases the clinical similarity to kuru is so striking—with progressive ataxia, incoordination, tremors, and dysarthria—that a comparison of these Western cases with kuru seems essential. 3 other cases appear to be more like classical paralysis agitans; 4 appear to be an acute syndrome with generalised muscular fasciculation, which may have an infectious ætiology; 2 cases with marked tremors suggest demyelinating cord syndromes with pyramidal-tract damage; and 2 others are apparently tremors secondary to traumatic lesions of the central nervous system from arrow wounds, with the upper motor-neurone syndrome also present. 1 further case is a typical senile tremor of moderate severity, while 3 others appear to be congenital non-progressive cerebellar tremors of the type we have called *kogaisantamba* in the kuru region. The remaining 6 patients have very fine constant tremors of non-congenital origin with no other symptoms.



To date no neuropathological examinations have been made since necropsies have not yet been possible. Thus the final decision as to whether or not any of these cases are pathologically akin to kuru must be postponed. The location of the kuru region and of the Wabag-Laiagam-Kundep tremor cases is indicated in the accompanying figure. These 24 patients with tremor (see table) have been observed in the Wabag-Laiagam-Kundep region over a period of about a year. They certainly represent several distinct nosological entities. The relationship of this variety of neurological syndromes to a number of well-known disorders is also not clear. The initial contact with these patients was such as not to permit the detailed clinical and pathological study which will be required for their more accurate classification. Similarly, in the Eastern Highlands the remarkable uniformity of the fatal kuru syndrome contrasts sharply with rarer sporadic cases of other neurological disorders involving tremors which have been identified in the kuru region.

Thus, in the Eastern kuru region we have reported a congenital non-fatal cerebellar tremor, called *tavaravain avie* or *kogaisa en avie*, by the Fore tribe and *kogaisantamba* by the Auiana tribe (Zigas and Gajdusek 1957, Gajdusek and Zigas 1958, 1959a), and in the Auiana linguistic group we have seen a strange, undiagnosable neurological disorder, called *tukesa* by some natives, involving a fine tremor, which is acute in onset and lasts several years without leading to death. Finally, a mass hysterical tremor associated with a cargo cult has occurred north of the kuru region among the Kamano people (Berndt 1952).

All of these new western cases have occurred in natives belonging to the Enga linguistic group—a large group of some 110,000 Highland Melanesians. In the Enga dialect of the Laiagam region the word *puriripiram*, which means to shiver, is used to designate the new syndromes as well. This closely parallels the use of the word kuru, which also means to shiver, by the Fore for the eastern disease. An alternative word, also used to describe shivering in the Enga language, is also applied to these new syndromes: *waruwaru*. Thus far we have been unable to elicit any tradition of these diseases in the population or any sorcery system associated with them. On the other hand individual patients offer elaborate supernatural explanations of their symptoms. 2 examples of kuru-like tremor syndromes are given below:

Case-records

Case 1.—Imbun; male, aged 23–24, from Tari'ok-Laiagam area. The patient is said to have been ill with slowly progressing tremors for eight to nine years. The onset of his illness is described as insidious by reliable observers, although the patient himself claims that initially he had an acute episode associated with vertigo. There has reputedly been no remission in his tremors or ataxia since the onset, but in the past three years their severity has progressively increased and mild dysarthria has progressed to severe impairment of speech. Locomotion has been reduced to a slow staggering gait, and tremors have increased considerably in violence over the past two years. At rest or during sleep he has no tremor.

The patient and his relatives offer the following explanation for his disorder: The patient's father was killed by an enemy group, and the murdered man's body was burned in a pile of kunai grass. The patient, then a young boy, was taken and reared by his father's murderers. When, as an adolescent,

he noted the onset of tremors he reasoned that his dead father was angry with him for having lived in peace with his murderer. The spirit of his dead father was thus wreaking vengeance upon the non-avenging son. The patient, therefore, left the group who had killed his father and went to live with another group. The man who was thereafter his guardian throughout his adolescence is a reliable informant and he confirms the above anamnesis.

Examination

The patient was a well-developed and well-nourished young man with a severe, rather coarse, irregular kuru-like tremor which became progessively more severe as he attempted to carry out motor commands. The tremor involved the head, neck, extremities, and trunk, and was particularly severe in the shoulder-girdle. He could walk without support with his feet widely spaced in a swaying ataxic gait, during which his tremors reached extreme proportions with increased amplitude and were accompanied by shock-like jerks and some choreiform movements. He reeled, swayed, and staggered in a fashion suggesting inebriation, but his ataxia and disturbance in balance was a less dramatic aspect of the clinical picture than is usually the case in kuru. The choreiform involuntary movements were, on the other hand, more violent than in kuru.

There were no abnormalities in systems other than the central nervous system. The cardiovascular and respiratory systems, especially, appeared within normal limits, and no abnormality of the abdomen, genitalia, mucosæ, or skin was noted. There was no lymphadenopathy. The parotid areas were bilaterally soft, non-tender but slightly swollen.

The Romberg test was positive with eyes open, and finger-to-finger, finger-to-nose, and heel-shin tests were seriously impaired by tremor and choreiform movements. Cranial nerves were intact. The fundi appeared normal and no nystagmus was present, although the tremors were so severe as to make ophthalmological examination very difficult. Some nystagmoid jerking of eyes was present. Deep tendon reflexes were somewhat hyperactive, but were bilaterally symmetrical, and no pathological reflexes were elicited. No sensory disturbances were detected. The patient demonstrated a moderate tendency to giggle and laugh, and was usually somewhat euphoric. He appeared to be of normal intelligence and was well oriented in time, place and person.

PATIENTS WITH TREMOR DISORDERS SEEN IN THE WABAG-LAIAGAM-KUNDEP REGION 1958–59

Syndrome	Case no.	Sex	Age (yr.)	Place	Area	Tremor	Ataxia	Dysarthria	Fibrillation	Upper-motor neurone syndrome	Duration of symptoms	Outcome	Remarks
Kuru-like tremor ..	1	M	24	Tari'ok	Laiagam	+	+	+	..	..	8–9 yr.	Slowly progressive degeneration	Under study
	2	M	28	Longap	Kundep	+	+	+	..	..	1 yr.	Progressive degeneration	,, ,,
	3	M	35	Wangapisanda	Laiagam	+	+	+	+	..	1 mo.	Death	Muscular fibrillations appeared late. Leprosy case on 4, 4-diaminodiphenyl sulphone therapy
Paralysis-agitans-like tremor	4	M	30	Raiagama	Wabag	+	+	..	..	..	4 yr.	Slowly porgressive	Parkinsonian-like rigidity and gait
	5	M	40	Gaurua	Kundep	+	..	..	..	..	10 yr.	Stationary	No follow-up yet possible
	6	M	38	Kiakau	,,	+	..	..	..	..	10 yr.	,,	,, ,, ,,
Acute muscular fasciculation the predominant symptom, and tremor secondary	7	F	35	Birip	Wabag	+	+	±	+	..	5 mos.	Slowly recovering	?? febrile onset. Generalised fasciculation subsided. Slight deltoid and pectoral muscle fasciculation remains
	8	M	33	Aipos	,,	+	±	±	+	..	8 mos.	Remission	Fasciculation and tremors subsided slowly after attaining maximum severity
	9	M	16	Raiagama	,,	+	+	..	+	..	2 mos.	Remission	Well, without tremors for past 3 mos.
	10	M	25	Poas	,,	+	+	..	+	..	2 mos.	Death	Bromide sedation for tremor led to bromism. ? febrile onset
Tremors associated with upper-motor-neurone syndrome and localised disturbances of muscular tone	11	M	28	Panduaga	Kundep	+	+	..	+	+	1 yr.	Progressive deterioration	Much like a demyelinating cord syndrome with signs of pyramidal-tract lesion
	12	F	45	Kiakau	,,	+	+	..	..	+	5 yr.	Progressive deterioration	Much like a demyelinating cord syndrome with signs of pyramidal-tract lesion
Tremors allegedly secondary to traumatic lesions of the central nervous system	13	M	35	Taliates	,,	+	..	..	..	+	15 yr.	Stationary	Mild right hemiplegia secondary to arrow wound through left orbit. Tremor largely in right upper spastic extremity
	14	M	26	Chirunki	Laiagam	+	+	..	..	+	20 yr.	,,	Very mild left hemiplegia with very fine generalised tremor
Senile tremor	15	M	70	,,	,,	+	..	..	..	..	5 yr.	Slowly progressive	Hands and head mostly involved
Congenital cerebellar tremors akin to *kogatisantamba* of kuru region	16	M	45	Muriraga	,,	+	..	..	..	..	45 yr.	Stationary	Generalised fine rest tremor. Paternal grandfather had similar tremor
	17	M	40	Laiagam	,,	+	..	..	..	..	40 yr.	,,	Generalised fine rest tremor
	18	M	65	Chirunki	,,	+	..	..	..	..	65 yr.	,,	Fine constant head tremor only. Mother had similar head tremor
Very fine constant tremors of non-congenital origin	19	M	30	Liop	,,	+	..	..	..	..	20 yr.	,,	Since boyhood has had fine head and upper extremity tremor
	20	M	19	Kiakau	Kundep	+	±	..	..	..	?	Asymptomatic	Very mild tremor of hands and trunk
	21	M	40	,,	,,	+	±	..	..	..	?	,,	Very mild tremor of hands and trunk
	22	M	55	,,	,,	+	±	..	..	..	?	,,	Very mild tremor of hands and trunk
	23	M	55	,,	,,	+	±	..	..	..	?	,,	Very mild tremor of hands and trunk
	24	M	40	,,	,,	+	..	..	..	..	?	,,	Very mild tremor of hands and trunk

Cerebrospinal fluid examination revealed normal dynamics and no pleocytosis. Pandy test was negative. Total protein 35 mg. per 100 ml.

Course

Over five months' observation the patient has remained essentially unchanged, except for a somewhat increased locomotor ataxia and an even more violent display of involuntary tremor and choreiform movements when called on to perform motor activities or emotionally stimulated. He resembles very closely patients in the second stage of kuru, although his tremors and involuntary shock-like jerks are more severe and his locomotor ataxia less severe than seen in kuru patients.

Case 2.—Itapingi; male, aged 25–28, from Longap-Kundep area. Onset of disease was about a year ago, with mild tremor developing insidiously as his first symptom. He had not previously been severely ill and could report no antecedent acute febrile ailment or encephalitis-like disease. Concomitantly with the mild tremor he noted difficulty of articulation which subsided in a few days, although the tremor persisted. His tremor disappears with rest or sleep and becomes more severe on emotional stimulation or motor activity. Ataxia has developed and dysarthria has reappeared.

The patient and his relatives attribute his disease to his acceptance of a smoke offered him by a visitor from an enemy group, a short while before the onset of his symptoms.

Examination

He was a well-developed and well-nourished man in no acute distress. He was well oriented in time, place, and person, cooperative, and of apparently normal intelligence. He had a coarse kuru-like tremor which seemed to affect mainly muscles involved in posture and balance and became more severe with intentional movements. Romberg test was positive. He could walk without the aid of a stick, but used one for preference, and his gait was faltering and unsteady, with swaying and weaving and wide placement of the feet. He had a severe intention tremor which did not subside as long as as he was standing or in a posture of unstable equilibrium. The tremor was greatest in head and shoulder-girdle, but also involved trunk and lower extremities. Finger-to-finger, finger-to-nose, and heel-shin tests were well executed in spite of the tremor. No sensory disturbances were detected. Cranial nerves were all intact, and muscle examination revealed no spasm, paresis, or paralysis. Reflexes were symmetrical and normally active; no abnormal responses were noted. Cardiorespiratory system was normal, and no abnormalities were detected in the abdomen. There was no lymphadenopathy. Skin and mucosæ were clear.

Cerebrospinal-fluid examination revealed normal dynamics and no pleocytosis or rise in protein.

Course

Over three months' clinical observation the patient's tremor and ataxia have increased somewhat in severity, and mild dysarthria is now evident. However, as in case 1, the tremor is a more prominent feature of his clinical picture than the ataxia in contrast to the usual situation in kuru.

Discussion

In case 1 the illness, while evidently progressively advancing, is already of eight to nine years' duration, and such a lengthy course has not been encountered in kuru. Attempts to elicit history of such kuru-like cases occurring earlier have been unsuccessful with 1 exception.

A very reliable informant, a relative of case 1, has described in detail an illness which he considered to be clinically identical with that of case 1 and which occurred in an aged woman of the same clan-group some fifteen to twenty years ago. In this woman, however, the disease progressed more rapidly and led to incapacity and death in about a year, the patient having developed progressive ataxia, violent tremors, and dysarthria akin to that of our patient. This is, to date, our only evidence that the kuru-like syndrome is not new in the Wabag-Laiagam-Kundep region.

Three middle-aged male patients showed a picture of classical parkinsonism (cases 4–6).

In the Wabag area we have seen 4 patients (cases 7–10) in whom tremors were secondary to a more dramatic generalised muscular fasciculation or fibrillation of acute onset. These were not seen early enough in their courses to exclude the possibility of acute febrile onset. 2 of the patients in fact said that they had fever before the onset of the muscular fasciculations and secondary tremors, but they have been afebrile while observed by us. There have been no encephalitic symptoms or signs of meningeal irritation. Over a period of two to eight months 2 of these cases have recovered completely, while a 3rd is nearing complete recovery. The 4th died after two months of illness. There was no evidence of contact between the cases and thus no suggestion of contagion. Muscle and joint pains have been associated with this fibrillation syndrome, and during recovery fibrillary twitchings may persist for a long time in certain muscle-groups (deltoid and pectoral). We have no evidence as to the ætiology of these rather similar cases. They suggest an infectious meningomyeloradiculitis or a myositis, quite possibly due to a virus. Serological studies on convalescent blood specimens are being made to investigate this.

In cases 11 and 12 (see table) signs of the upper-motor-neurone syndrome with hyperactive deep tendon jerks, positive Babinski and Oppenheim reactions, and ankle clonus (patellar clonus as well in case 11) were elicited, and there was much spasticity (case 11) or plasticity (case 12) of the legs in which the tremors were most severe. These cases as well as cases 13 and 14, who reported old arrow wounds which had penetrated the cranium and who had spastic hemiplegias associated with distinct, regular tremors, particularly in the involved limbs, will be discussed in a later publication. Nevertheless there is very little similarity between the neurological disturbances in these cases and those of kuru.

Furthermore, in this Western Highlands region we have found 3 cases of long-standing non-progressive cerebellar tremor in men, dating from their infancy and clinically akin to the congenital cerebellar tremors of the kuru region and adjacent areas (cases 16–18 of the table). 2 of these patients with congenital cerebellar tremor, similar to *kogaisantamba*, have family histories of the disease reported in near relatives (the mother of one patient and the paternal grandfather of another). In no case does the condition interfere with normal participation in the social life of the community.

Finally, the case of senile tremor (case 15) and the 6 cases of mild generalised tremors (cases 19–24) with slight yet detectable ataxia in middle-aged men have been included for the sake of completeness, and we intend to follow the progress of these cases.

The largest number of cases with tremor syndromes have come from remote primitive regions, particularly the Kundep, an uncontrolled area south-east of Laiagam patrol post (Meggitt 1956). A patrol post will be established there this year, which will bring administrative authority to the region for the first time. Investigation of most of the cases has thus been restricted to examination out of doors beside the primitive native houses or on singsing grounds located among the men's and women's houses. Such examinations have been conducted without the aid of laboratory facilities or any but the most simple

neurological instruments. We have searched for further foci of these tremor syndromes throughout the uncontrolled Kundep region, and now believe that, although the area has not been completely explored, there is no large undiscovered centre of kuru-like disease. All the cases live over 7000 ft. above sea level in the cool region of dense rain forests and swampy kunai slopes and river valleys. Malaria is unknown here, and mosquito-borne diseases are unlikely.

Motion-picture (16 mm.) records of all the cases have been made and the kuru-like *puriripiram* (*waruwaru*) cases have been compared with kuru on the cine record.

The implications of these newly discovered neurological disorders for the kuru problem are great. On the one hand the clinical picture in cases 1–3 may represent a totally different illness, bearing no relation to kuru, but strangely akin to it. Conversely some of these new *puriripiram* syndromes may be clinical variants of kuru and related to it in pathogenesis. The latter is suggested by the clinical picture if not by the epidemiology of the disease. If the genetic hypotheses are correct, Melanesian natives may possibly have an unstable locus in their chromosomes at which mutation to produce inborn defects of metabolism leading to cerebellar, basal-ganglionic and generalised central-nervous-system, diseases of the kuru type is likelier than among other races. The unusually high incidence of tremor disorders in this small population surveyed and the presence in the Eastern Highlands of the unique kuru with, here in the Western Highlands, another new, somewhat kuru-like disorder might suggest this. The possibility of genetic kinship between the Fore people of the Kuru region and the distant Enga-speaking people seems remote, but further study is essential. If such a kinship could be established, then a single kuru mutation might be assumed to underlie both syndromes. Even so, the ethnoenvironmental variables which determine altered clinical and epidemiological expression must still be elucidated. With this in mind and with the added stimulus of the suggestion that there is a distinct resemblance between kuru and scrapie in sheep (Hadlow 1959) our future studies at the Kuru Research Centre will be concerned with further investigation of possible infectious, toxic, or deficiency factors underlying kuru, and with investigations of intermediary metabolism in both kuru and the Western Highlands diseases.

We are deeply indebted to Dr. Leo Petrauskad, District Medical Officer, Mount Hagen, for his support and assistance and alert forwarding of patients to the Kuru Research Centre at Kainantu. European Medical Assistant Ken Mitchell and Patrol Officer Grahame H. Pople of Laiagam have contributed valuable observations and assistance to the study of these new syndromes, and District Commissioner Ian Skinner and District Officer S. M. Foley of Mount Hagen have rendered assistance and encouragement without which the work could not possibly have been conducted.

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EXCRETION OF FORMIMINOGLUTAMIC ACID AS AN INDEX OF FOLIC-ACID DEFICIENCY

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SEVERAL recent studies (Broquist 1956, Silverman, Gardiner, and Condit 1958, Broquist and Luhby 1959) have indicated that formiminoglutamic acid, an intermediate product in the metabolic breakdown of histidine, accumulates in the urine of both human subjects and rats which are deficient in folic acid (i.e., pteroylglutamic acid or its derivatives). All methods at present available for the detection of folic-acid deficiency in man depend on the measurement of the levels of folic acid in blood and urine after the administration of test doses of pteroylglutamic acid or a derivative (Spray 1956). Although these tests provide much useful information, they are open to the objections common to all saturation tests, and a more physiological test is needed. We report here the preliminary results of using the urinary excretion of formiminoglutamic acid as an index of folic-acid deficiency.

Methods

As control subjects, seven healthy medical and laboratory workers were studied—three men and four women aged between 26 and 48. The patients (tables I and II) included two women with pernicious anæmia of pregnancy, two women with megaloblastic anæmia which had not responded to treatment with vitamin B_{12}, two men and one woman with untreated pernicious anæmia, and three women suffering from megaloblastic anæmia due to other causes.

Each subject was asked to collect all urine passed during 24 hours, after which histidine hydrochloride 2 g., dissolved in about 100 ml. water, was given by mouth. A second sample of urine was collected during the 24 hours immediately following the dose. Urine was collected in glass bottles without preservative; the volume of each sample was recorded and about 20 ml. was stored frozen until required for assay.

The formiminoglutamic-acid activity of each sample was estimated by the method of Silverman, Gardiner, and Condit (1958).

A buffered solution containing pteroylglutamic acid is incubated with an extract of fowl liver to reduce the pteroylglutamic acid to tetrahydro-pteroylglutamic acid. Suitable amounts of urine are then added to the incubated mixtures, and incubation is continued, so that the formiminoglutamic acid in the urine reacts with the tetrahydro-pteroylglutamic acid to form N^{10}-formyl-tetrahydro-pteroylglutamic acid. By autoclaving in the presence of ascorbic acid this is converted to the citrovorum factor, which is then assayed microbiologically.

Results are expressed as milligrammes of formiminoglutamic acid excreted in 24 hours, the yield of citrovorum factor being converted into terms of formiminoglutamic acid on the assumption that the reaction is quantitative.

Results

Four of the control subjects showed no formiminoglutamic-acid activity in the urine either before or after histidine, and only very small amounts of activity were found in the others (table III). These low figures are of doubtful significance because the levels of citrovorum-factor activity from which they are derived are very close to those of the reaction mixtures to which no urine is added.

Three of the four patients who appeared clinically to be deficient in folic acid showed an increased excretion of

TABLE I—MEGALOBLASTIC ANÆMIA APPARENTLY DUE TO DEFICIENCY OF FOLIC ACID

Patient	Sex	Age (yr.)	Diagnosis	Serum-vitamin B_{12} ($\mu\mu$g. per ml.)*	Treatment	No. of days on treatment	Hæmoglobin (g. per 100 ml.)		Maximum reticulocytosis	
							Before treatment	After treatment	%	Day observed
1	F	27	Pernicious anæmia of pregnancy	100	Folic acid 40 mg. daily	10	5·2	7·4	28	7
2	F	29	Pernicious anæmia of pregnancy	250	Folic acid 45 mg. daily	11	8·9	11·1	16	5
3	F	74	Idiopathic steatorrhœa	85	(i) Vitamin B_{12} 100 μg. daily	8	8·2	6·4	3	8
					(ii) Folic acid 30 mg. daily	23	6·4	9·4	29	11
4	F	75	Diaphragmatic hernia and dietary deficiency	240	(i) Vitamin B_{12} 1000 μg. one dose	14	11·7	8·1	1·5	14
					(ii) Folic acid 30 mg. intramuscularly b.d. for five doses	8	8·1	9·2	12	6
					(iii) Folic acid 30 mg. b.d. by mouth, 30 mg. daily intramuscularly	29	9·2	10·1	4·5	13

* Normal range 150-1000 $\mu\mu$g. per ml.

activity before histidine, but the other (patient no. 2) excreted a comparatively small amount. On the other hand, both this patient and the other two who were studied after receiving a dose of histidine showed high levels of activity in the second 24-hour period (table IV). All these patients gave satisfactory hæmopoietic responses to treatment with pteroylglutamic acid, and previous treatment with vitamin B_{12} failed to provoke any response in patients nos. 3 and 4 (table I). These findings provide additional evidence that the patients were suffering from deficiency of folic acid. When the tests were repeated after treatment, the excretion of activity was greatly reduced (table IV).

None of the patients who appeared to be suffering from deficiency of vitamin B_{12} excreted nearly as much activity as those with deficiency of folic acid (table V). In some instances the excretion was higher than found in any of the control subjects studied, but it was never higher than found after treatment in the patients who had had folic-acid deficiency. Table II shows that all but one of these patients whose anæmia seemed to be due to vitamin-B_{12} deficiency showed satisfactory responses to treatment with this vitamin. The patient (no. 10) who did not respond was suffering from megaloblastic anæmia after partial gastrectomy 15 years previously, and she did not respond to pteroylglutamic acid. This lack of response to either vitamin was probably due to deficiency of iron, since she had a low serum-iron and her peripheral blood showed well-marked changes of iron deficiency. Nevertheless, because of the low level of vitamin B_{12} in her serum, and because she absorbed only 12% of an oral dose of 0·5 μg. ^{58}Co-vitamin B_{12}, we attribute her megaloblastic anæmia to deficiency of vitamin B_{12}. Badenoch, Evans, Richards, and Witts (1955) reported similar poor responses to vitamin B_{12} and pteroylglutamic acid in two patients with megaloblastic anæmia after partial gastrectomy.

Discussion

The results show that patients suffering from a deficiency of folic acid excrete in the urine much greater amounts of formiminoglutamic-acid activity than either normal subjects or patients with megaloblastic anæmia due to deficiency of vitamin B_{12}. After treatment with pteroylglutamic acid, the amount of activity excreted by these patients was much reduced, so that the high levels before treatment appear to be the direct results of a deficiency of folic acid. Results similar to those which

TABLE III—EXCRETION OF FORMIMINOGLUTAMIC ACID IN NORMAL SUBJECTS BEFORE AND AFTER A TEST DOSE OF 2 G. HISTIDINE HYDROCHLORIDE BY MOUTH

Subject no.	Sex	Age (yr.)	Formiminoglutamic-acid activity excreted in the urine in 24 hours (mg.)	
			Before histidine	After histidine
11	M	29	0	0
12	M	48	0	0
13	M	39	0	0
14	F	34	0	0·16
15	F	45	0	..
16	F	35	0	0
17	F	26	0·19	0·23

TABLE II—MEGALOBLASTIC ANÆMIA APPARENTLY DUE TO DEFICIENCY OF VITAMIN B_{12}

Patient	Sex	Age (yr.)	Diagnosis	Serum-vitamin B_{12} ($\mu\mu$g. per ml.)*	Treatment	No. of days on treatment	Hæmoglobin (g. per 100 ml.)		Maximum reticulocytosis	
							Before treatment	After treatment	%	Day observed
5	F	27	Megaloblastic anæmia following massive intestinal resections	50	Vitamin B_{12} 100 μg. daily	9	11·2	13·0	19	7
6	F	66	Untreated pernicious anæmia	48	Vitamin B_{12} 100 μg. daily	13	9·3	11·9	30	7
7	M	44	Untreated pernicious anæmia	10	Vitamin B_{12} 100 μg. daily	13	5·1	9·3	55	5
8	M	72	Untreated pernicious anæmia	35	Vitamin B_{12} 100 μg. twice weekly	38	7·2	12·3	..	..
9	F	22	Megaloblastic anæmia due to anticonvulsants	140	Vitamin B_{12} 100 μg. daily	15	5·7	9·4	13	9
10	F	59	Megaloblastic anæmia after partial gastrectomy	44	(i) Vitamin B_{12} 100 μg. daily	10	7·4	6·8	7·3	7
					(ii) Folic acid 45 mg. daily	7	6·8	7·1	2·4	7

TABLE IV—EXCRETION OF FORMIMINOGLUTAMIC ACID IN PATIENTS WITH FOLIC-ACID DEFICIENCY BEFORE AND AFTER A TEST DOSE OF 2 G. HISTIDINE HYDROCHLORIDE BY MOUTH

Patient no.	Formiminoglutamic-acid activity excreted in the urine in 24 hours (mg.)			
	Before treatment		After treatment with folic acid	
	Before histidine	After histidine	Before histidine	After histidine
1	32	..	..	..
2	2·0	11	1·1	0·37
3	7·9*	18*	0·21	0·74
4	19	50	0·51	1·6

* These results were obtained from incomplete collections as the patient was incontinent.

TABLE V—EXCRETION OF FORMIMINOGLUTAMIC ACID IN PATIENTS WITH DEFICIENCY OF VITAMIN B_{12} BEFORE AND AFTER A TEST DOSE OF 2 G. HISTIDINE HYDROCHLORIDE BY MOUTH

Patient no.	Formiminoglutamic acid activity excreted in the urine in 24 hours (mg.)	
	Before histidine	After histidine
5	0	1·1
6	0·18	0·24
7	0·97	0·71
8	0·46	1·3
9	0	0·36
10	0·33	1·9

we obtained in the two patients with pernicious anæmia of pregnancy have been reported in a small number of similar patients by Luhby, Cooperman, Teller, and Donnenfeld (1958) and Broquist and Luhby (1959).

While it is difficult to generalise from such a small number of results, it appears that a gross deficiency of folic acid, sufficient to cause frank megaloblastic anæmia, is necessary before a patient shows an increased excretion of formiminoglutamic acid. This is supported by the fact that three or four pregnant women with mild anæmia and megaloid changes in the bone-marrow, suggestive of mild deficiency, did not show increased excretion even in response to histidine. These results are not included in the tables. In addition, several authors have produced evidence suggesting that in untreated pernicious anæmia there is a secondary deficiency of folic acid (Spray 1956), but our results indicate that this deficiency is insufficient to cause increased excretion of formiminoglutamic acid.

The limitations of the method of estimation, and the identity of the activity measured, must be considered in interpreting the results.

It has not been possible so far to obtain any pure formiminoglutamic acid to use as a standard to check the accuracy of the estimations. Repeated estimations on the same sample of urine have shown that individual results may sometimes differ by as much as 100%, although the reproducibility is usually better than this. Silverman et al. (1958) publish a single set of observations which suggest a much greater degree of accuracy than we have been able to obtain. Hence we feel that only those results which are at least three times higher than any found in subjects not suffering from deficiency of folic acid are to be regarded as significant.

Silverman et al. (1958) show that certain substances other than formiminoglutamic acid can give a positive result by this method. Thus the identification of the activity we have measured as formiminoglutamic acid rests on indirect evidence, such as the comparison of its behaviour in the assay procedure with that of pure formiminoglutamic acid, and its destruction under conditions which destroy pure formiminoglutamic acid. We have not tested all samples of urine under such conditions, but all but one of several samples treated as described by Tabor and Wyngarden (1958), by autoclaving in the presence of alkali, showed complete loss of activity.

In spite of these possible objections, the method used obviously estimates some substance which behaves like formiminoglutamic acid, which is excreted in excessive amounts in patients suffering from deficiency of folic acid, and the excretion of which is greatly reduced when the patients are treated with pteroylglutamic acid. On these grounds alone, the test should be a useful additional tool in the investigation of the megaloblastic anæmias, although more results are required before its value can be assessed critically. Since some patients, such as no. 2, only show increased excretion of activity after receiving histidine, it seems likely that enough information can be obtained, and the test thereby simplified, by collecting a single sample of urine during the 24 hours after the histidine has been given.

Summary

The urinary excretion of formiminoglutamic acid, an intermediate in the metabolic breakdown of histidine, has been measured before and after an oral dose of histidine in seven normal subjects, four patients with megaloblastic anæmia due to deficiency of folic acid, and six patients with megaloblastic anæmia due to deficiency of vitamin B_{12}.

The patients with folic-acid deficiency excreted much larger quantities of formiminoglutamic acid than either the normal subjects or the patients suffering from deficiency of vitamin B_{12}. After treatment with pteroylglutamic acid, the excretion fell to levels comparable with those found in the other groups.

This test may provide a useful additional tool in the investigation of the megaloblastic anæmias.

We are grateful to Miss Janet Nelson for assistance with the experimental work; to Miss Barbara Mallett, B.SC., for the hæmatological data; and to Sir George Pickering and Dr. E. M. Buzzard for allowing us to investigate patients no. 4 and 10 respectively. The work was in part supported by a grant from the Medical Research Council to L. J. W.

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DIALYTIC PARABIOSIS

A New Method of Treating Renal Failure by the Extrarenal Route, Using a Mammalian Donor

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REMARKABLE advances in the management of acute renal failure have been achieved in recent years, thanks to improvements in conservative medical treatment and to the introduction of artificial measures, including cross-circulation and various procedures involving dialysis.

Cross-circulation, which temporarily connects the blood-stream of a uræmic patient with that of a normal person, is, in theory, the best method. But it is seldom applied because of the difficulty in finding a willing normal subject whose blood-group is compatible, and because there is possible danger to the donor.

Various dialysis techniques have become popular and have found a place in the treatment of renal failure. But even the artificial kidney, which is the most efficient instrument, is not free from imperfections.

The bath fluid is an artificial solution of essential electrolytes, and its similarity to normal plasma is only approximate. During treatment not only harmful material is removed but also other diffusible substances which are useful or necessary for maintaining life, such as vitamins, coenzymes, essential aminoacids, and trace elements. Such losses might be important, especially when several dialytic treatments are applied, and they might explain why the lives of uræmic patients cannot be prolonged beyond a relatively short time, even when blood non-protein nitrogen (N.P.N.) is kept comparatively low. Altieri et al. (1956) showed experimentally that vitamins are diffusible, and Begani (1955) and Edwards and White (1959) observed loss of antibiotics during dialysis. Further investigation is desirable.

To avoid any loss of vital substances, Bessis and Freixa (1949) used horse-blood experimentally as the bath fluid. But this cannot be used clinically because of the difficulty of collecting the enormous amount required to fill the artificial kidney.

Krainin (1952), Salisbury (1958), and Pavone-Macaluso (1957a), working independently, have designed a technique (called cross-dialysis by Krainin, and dialytic parabiosis by Pavone-Macaluso) which makes a new approach to the problem. This technique, which has been compared to an artificial placenta, allows transfer between the recipient and the donor, without any mixing of blood, across a dialysing membrane. The cellulose membrane is permeable to water, electrolytes, urea, and other small molecules, but it is impermeable to colloidal solutes, such as proteins or other substances with antigenic properties. The bath fluid is a small volume of plasma, the composition of which is kept constant by the donor.

In the first experiments dogs only were used (Krainin 1952), and the blood from the donor and the blood from the anuric animal were circulated inside two different 'Cellophane' tubes, tightly wrapped together. Pavone-Macaluso (1957b) was the first to describe similar experiments performed upon animals of different species, using the same principle but a slightly different technique.

Our early experiments were made in vitro, working on various artificial solutions. A small apparatus was used, consisting of two cellulose tubes, wrapped spirally around a metal-net cylinder, and enclosed within a narrow space between two glass cylinders, one inside the other. A solution of diffusible material (a dye or urea) was circulated through one of the cellulose tubes, while distilled water flowed through the second tube. The space between the cylinders was filled with a small volume of distilled water. The substance under test shifted rapidly into the bath fluid, and then circulated inside the second cellulose tube. Further experiments, based on the same principle, were made on pairs of dogs or rabbits and lastly on pairs of animals of different species—e.g., dogs and goats (fig. 1). Ox plasma or Ringer's solution mixed with 'Macrodex' was used as a "transferring fluid". When dialytic parabiosis was brought about between a kid and a dog, which was sensitised to the kid's proteins, no signs of anaphylaxis or intolerance were observed, and the blood-pressure was normal throughout (Pavone-Macaluso and Allegra 1958).

Salisbury, in 1952, has also made some interesting experiments, which unfortunately have not been published (Salisbury 1958). Animals of different species—i.e., dogs and goats (large males, weighing about 180 lb.)—were used. The goat's blood was circulated through the "solution compartment" of a Skeggs-Leonards dialyser, and the dog's blood was circulated in the "blood compartment". This cross-dialysis was well tolerated.

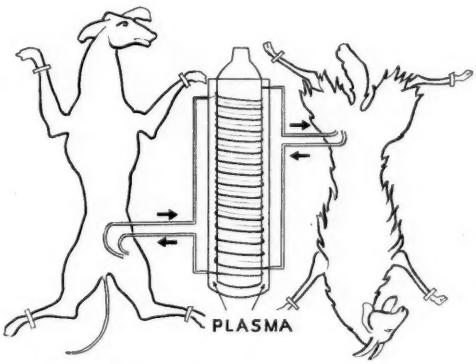

Fig. 1—Dialytic parabiosis between a dog and a goat.

This experimental work shows that during dialytic parabiosis blood N.P.N. is significantly lowered in the anuric recipient, and slightly increased in the healthy donor in which diuresis is stimulated, especially some hours after treatment has been stopped; and the anuric animal's abnormal electrolyte patten improves. Dialytic parabiosis can be safely accomplished between animals of different species. Its main advantage is that the healthy donor, whose regulating properties (chiefly renal function) are normal, is able to react against any artificial alteration produced. The donor removes harmful material and may also give some essential factors. Dialytic parabiosis may be of therapeutic value therefore not only in the treatment of uræmia but also in liver diseases where the artificial kidney is of little value (Salisbury 1958).

This method was used in a case of severe uræmia due to mercury poisoning, which was considered incurable. The mammalian donor was a sheep.

Case-report

A woman of 34 had swallowed an unknown amount of mercuric bichloride which produced anuria and ulcerous gastroenteritis, with bloody diarrhœa. She was admitted to hospital after 3 days' anuria.

The findings were: blood N.P.N. 147 mg. per 100 ml., Na 134 mEq. per litre, K 3·6, Cl 91, and HCO_3 22; specific gravity of plasma 1026; blood-pressure 135/70 mm. Hg; pulse-rate 96 per min.; and body-weight 155 lb. There was no peripheral œdema, and no sign of fluid retention detectable radiologically. The kidneys were enlarged, and there was a gingival "line".

Dimercaprol (BAL) was given, and a careful control of fluid, salt, and acid-base balance was started. After 7 days' anuria, the N.P.N. had risen to 260, the diarrhœa had almost stopped and the prognosis looked hopeless. Treatment by dialytic parabiosis was planned, but, because of the onset of menstruation which continued for 3 days, it was delayed to avoid risks from heparinisation. Meanwhile some urine was produced and the daily output rapidly increased. On the 11th day, the urine-volume was 300 ml., but the N.P.N. was 360 mg. per 100 ml., and the patient's condition was deteriorating. We decided therefore to dialyse her blood immediately, because it seemed that the only chance of survival lay in prolonging her life until diuresis could produce satisfactory clearance. Methyl ergometrine malleate ('Methergin', Sandoz) was given first to obtain uterine hæmostasis.

Technical Data

The disposable dialysing unit of a Kolff-Watschinger twin-coil kidney, although made for a different purpose, was used. It consists of two parallel cellulose tubes, 10 metres long with a surface area of

9000 sq. cm. A plastic net stops the swelling of the cellolose tubes, and allows the unit to be kept in a comparatively small space. The lower opening of the container was closed, and two holes, through which the inner connecting tubes pass (fig. 2), were plugged by two perforated rubber stoppers. The container was then filled with 1·5 litres of plasma diluted with an equal volume of 5% glucose-saline. The connecting tubes were lengthened by silicone-rubber tubes.

The upper cellophane coil, as well as the related connecting tubes, were filled with 500 ml. of compatible human blood. The Battezzati-Taddei artificial-kidney pump was fixed to the inward connecting tube, and a blood-filter was inserted in the outward tube (fig. 3). To prepare the lower coil for the donor the empty spaces were filled with Ringer's solution mixed with macrodex. The free ends of two large 'Polystan' cannulæ and two glass cannulæ were inserted into short silicone-rubber tubes, closed by means of clamps, and filled with saline containing a small amount of heparin.

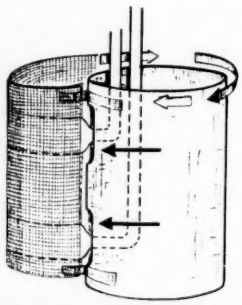

Fig. 2—Detail of the disposable unit of the Kolff-Watschinger twin-coil kidney, used for dialytic parabiosis.

The arrows show the inner holes to be plugged. (Modified from Watschinger 1957.)

The Dialysis

The donor was a large ewe, weighing about 130 lb. It was tied supine over a transportable bed. The carotid artery and the jugular vein were isolated surgically, and the polystan cannulæ were inserted.

The patient was in another room. The glass cannulæ were introduced into the radial artery and into a vein of the same forearm. The sheep was brought in, covered with a sheet, to hide it from the patient.

After the sheep had been given heparin, its blood was allowed to circulate through the lower cellophane circuit.

The patient was given heparin, 150 mg., and the dialytic parabiosis was started, the patient's blood circulation-rate being about 250 ml. per min. Because there was an almost immediate drop in systolic blood-pressure, from 135 to 80 mm. Hg, the circulation was interrupted, and macrodex was given intravenously. After 10 minutes the patient vomited some bloodstained fluid, and then the blood-pressure rose gradually to normal. Despite the apprehension which this episode caused, we decided to continue.

The coagulation-time was controlled every 15 minutes, and small amounts of heparin were given when necessary. Everything had been satisfactory for 90 minutes, when the patient collapsed again. The dialysis was stopped immediately, and a blood-transfusion was given. Fortunately, the blood-pressure returned to normal after 15 minutes. The patient again vomited blood. Although the treatment had been much shorter than was planned, we decided not to continue.

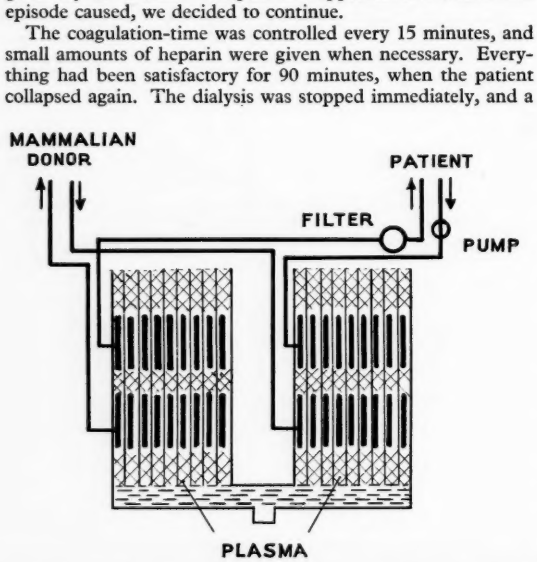

Fig. 3—Schema of dialytic parabiosis between a patient and a mammalian donor, using a Kolff-Watschinger coil kidney.

Course after Dialysis

The biochemical data before and after dialysis (which lasted 90 minutes) are as follows:

—	Patient's blood		Sheep's blood		Bath fluid	
	Before	After	Before	After	Before	After
N.P.N. (mg. per 100 ml.)	360	280	28	34	11	58
Na (mEq. per litre)	119	135	140	142	145	140
K " " ..	5·4	4·5	4·2	4·3	3·5	4·3
Cl " " ..	88	93	101	120	138	122
HCO_3 " " ..	17·8	19·7	25	24	15	20·3

The patient's general condition did not change noticeably after dialysis. A few hours later she vomited a large amount of a black fluid containing altered blood. Melæna was observed next day, and another transfusion was given. Meanwhile the urine-volume increased rapidly. On the 3rd day after dialysis—i.e., the 14th day after the onset of anuria—the urinary output had reached 1800 ml. The urine was still of low specific gravity and contained 8 g. per litre of urea. On the 5th day after dialysis, there was a diuresis of 2300 ml., but the blood N.P.N. had risen again to 390 mg. per 100 ml., although the patient's condition was satisfactory, because of careful control of fluid/salt balance throughout the postanuric stage. A peritoneal lavage was planned (instead of another dialytic parabiosis, which would involve the risk of further heparinisation), but a spontaneous gradual fall in the blood N.P.N. started, and this treatment was therefore not needed.

The patient made a complete recovery within 2 months.

Discussion

This first clinical application of dialytic parabiosis was satisfactory. The collapses during treatment cannot be related to absorption of "toxic" substances from the animal. The first occurred before there was time for such hypothetical substances to reach an adequate concentration in the bath fluid and to diffuse into the patient's blood. Furthermore, she recovered quickly when macrodex was given, and she did not collapse again when the treatment was started again. Both episodes occurred soon after heparin was given, and they were both followed by the vomiting of bloodstained material. The later hæmatemesis and melæna were strongly suggestive of intestinal bleeding, which was likely to be due to heparinisation further complicating the ulcerous enteritis which had previously produced bloody diarrhœa.

Though the period of dialysis was short, the blood N.P.N. was significantly lowered, and the abnormal electrolyte pattern was much improved. Though definite conclusions cannot be drawn from a single case, we may assume that, by prolonging the dialysis, the results may be better in uncomplicated cases.

Summary

The principle of dialytic parabiosis, and the experimental results, are described.

A woman who developed total anuria following mercury poisoning was treated by dialytic parabiosis, using a large sheep as donor, and diluted plasma as the bath fluid. The disposable unit of a Kolff-Watschinger twin-coil artificial kidney was adapted for this purpose. The treatment was stopped after 90 minutes, because of collapse following an intestinal hæmorrhage, but there was a significant fall in blood non-protein nitrogen, and a considerable improvement in the abnormal electrolyte pattern. After a diuresis, the patient recovered.

We are grateful to Prof. N. Alwall (Renal Clinic, Lund) and Prof. P. Caselli (Institute of General Pathology, Palermo) for experimental resources; to Prof. F. Ferina, Dr. P. Monaco, Dr. F. Goria, Mr. L. Allegra (Palermo), and the technical staff of the renal clinic of Lund University, for cooperation in the experimental work; to Prof. A. Mirri (Zooprophylactic Institute, Palermo) for kindly supplying the sheep; and to Dr. A. Manzo and Dr. V. La Grutta (Palermo) for helping with laboratory data.

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PITUITARY TUMOURS MANIFESTED AFTER ADRENALECTOMY FOR CUSHING'S SYNDROME

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MANY patients with Cushing's syndrome derive striking benefit from adrenalectomy (Montgomery and Welbourn 1957). For this reason less attention is paid now than formerly to the possible role of the pituitary gland in the pathogenesis of the disease. It may well be less important than Cushing (1932) believed, but adenomas (two-thirds of them basophil) are present in about half the patients (Thompson and Eisenhardt 1943, Plotz et al. 1952). Most of them are small and cannot be detected during life, except at hypophysectomy. A few, however, cause enlargement of the sella turcica. This was detected by radiography in 12 out of 153 cases at the Mayo Clinic (Rynearson 1958) and in 1 out of 20 cases of our own (Welbourn 1958, 1959). Possibly most patients die from the general effects of the disease before the tumour has time to grow to a large size.

Carcinoma of the pituitary associated with Cushing's syndrome has been described on at least 6 occasions. In 3 of these the cells were basophil (Cohen and Dible 1936, Sheldon et al. 1954, Browne et al. 1955), in 2 they were chromophobe (Salus 1933, Feiring et al. 1953), and in 1 both chromophobe and eosinophil cells were present (Forbes 1947). In 3 cases (Cohen and Dible 1936, Forbes 1947, Sheldon et al. 1954) there were metastases in the liver.

We have been concerned for some time lest pituitary tumours might continue to grow and ultimately cause trouble in those whose lives are prolonged by adrenalectomy. Reports are now beginning to appear which indicate that this may indeed be the case.

Siebenmann (1955) reported the case of a woman of 27 who developed addisonian pigmentation and suffered an adrenal crisis one year after subtotal adrenalectomy. A year later the syndrome recurred and the patient developed morbid hunger, bouts of excessive thirst, and signs of chiasmal compression. There was no radiographic evidence of enlargement of the sella. She died after removal of the adrenal remnant, and at necropsy was found to have a " mixed-cell basophilic-chromophobic adenoma " of the anterior lobe of the pituitary. The tumour was the size of a hazel nut, and had extended out of the sella and beneath the brain in the form of a mushroom.

A similar case was reported by Glenn et al. (1958). Three years after subtotal adrenalectomy the patient suddenly developed right-sided ophthalmoplegia, bitemporal hemianopia, and diabetes insipidus. Radiography showed enlargement of the sella, and blood was present in the cerebrospinal fluid. The appearances at craniotomy were consistent with bleeding into a pituitary adenoma. No further details are given.

Harrison (1958) and Nelson et al. (1958) recorded 1 case (a woman of 33), out of a total of 25 who had undergone total adrenalectomy, who developed severe pigmentation and failing vision three years after operation. The sella was enlarged radiologically. Very high levels of corticotrophin were found in the blood, and the urinary excretion of melanocyte-stimulating hormone (M.S.H.) was greatly in excess of normal. Irradiation of the pituitary area was followed by headaches and complete blindness. At craniotomy a large chromophobe adenoma was partly removed. A further course of irradiation was given and the patient improved. The eyesight returned to normal and the pigmentation regressed considerably.

Rees and Bayliss (1959) report another case. A man of 28 suffered a relapse of Cushing's syndrome, associated with pigmentation, two years after subtotal adrenalectomy. A further remission was induced by removal of the hypertrophied adrenal remnant. Eighteen months later he was deeply pigmented and the dorsum sellæ was decalcified. High levels of corticotrophin and of M.S.H. were found in the blood. A year later a basophil adenoma was removed from the pituitary and the pigmentation started to fade.

Walters (1958) reports that pituitary tumours became manifest after operation in several cases at the Mayo Clinic. One was a chromophobe adenoma (Kernohan and Sayre 1956) and another a malignant tumour with extracranial metastases.

We report here two cases of Cushing's syndrome in which pituitary tumours became manifest some time after adrenalectomy. Both were transitional-basophil in type. One was malignant and resulted in death. The other was probably benign and was removed surgically.

Case-reports

THE FIRST CASE

The patient (Montgomery and Welbourn 1957, case 7), a girl of 15, was first referred to hospital in 1954 as a probable case of Cushing's syndrome. She complained of excessive gain of weight from the age of 10, and of delay in the onset of her periods.

Examination

She was a short girl with a round plethoric face, obesity confined to the trunk, and purple striæ over the lower abdomen and flanks. There was a little increase in peripheral hair growth, and the pubic hair had a masculine distribution, but there was no facial hirsutism. The blood-pressure varied from 140/90 to 170/110 mm. Hg. The central nervous system was normal, and there was no bone tenderness or disturbance of the gastro-intestinal tract. Pelvic examination was negative and the clitoris was not enlarged.

Investigations

Radiography of the chest was normal, and skull X-ray showed no enlargement of the pituitary fossa. Adrenal tomography, combined with presacral insufflation of oxygen and intravenous pyelography, revealed no apparent enlargement of the adrenal glands. X-ray of the lumbosacral spine did not

show osteoporosis, but the serum-calcium level was 11·3 mg. per 100 ml.

A fractional test-meal revealed hyperacidity with free HCl rising to 115 clinical units. The hæmoglobin level was 14·8 g. per 100 ml. and the white-blood-cell count was 12,600 per c.mm. The serum-electrolytes and fasting blood-sugar were normal.

The urinary excretion of 17-hydroxycorticoids was 26·9 mg. per twenty-four hours in the resting state, and 52·7 mg. per twenty-four hours during stimulation with 25 mg. of corticotrophin intravenously.

Treatment

Cushing's syndrome, with probable adrenocortical hyperplasia, was diagnosed and operation advised. 90% of the left adrenal gland was resected on Oct. 1, 1954, and the whole of the right gland was removed eleven days later. The weights of the resected portions were 4·7 g. and 6·9 g. respectively. An adrenal crisis followed the first operation (before which no substitution therapy had been given), but this responded to treatment with noradrenaline and cortisone.

The patient recovered rapidly, and cortisone was stopped after six weeks. A remission of the Cushing's syndrome followed, although strict dieting was required to reduce the patient's girth. The blood-pressure fell steadily to 120–130/75–80. The facial appearance returned to normal, the hair became lighter, the striæ faded, and the periods started to come regularly.

Course

Dark pigmentation developed in the operation scar and stitch marks within a few weeks of operation, and never faded. About eighteen months after operation, pigmentation of a typically addisonian type began to appear, and by August, 1956, it was very pronounced on the face, hands (especially in the creases), arms, shoulders, and elbows, and in the mouth (see Montgomery and Welbourn 1957, fig. 183). This was interpreted as evidence of adrenal insufficiency, although there was no loss of energy or appetite, no hypotension, and no electrolyte disturbance. However, no 17-ketosteroids or 17-ketogenic steroids could be detected in the urine either in the basal state or following stimulation for four days with 20 mg. of corticotrophin gel twice daily. Consequently, in January, 1957, cortisone 12·5 mg. daily by mouth was started, and later the dosage was doubled when it was found that the pigmentation was unchanged.

In August the patient began to complain of pain affecting the left side of her face, neck and forehead, and the eye and ear on the same side. No cause could be found. There was no gross diminution of the visual fields. Although it was not appreciated at the time, an X-ray of the sinuses, taken in October, revealed enlargement of the sella turcica.

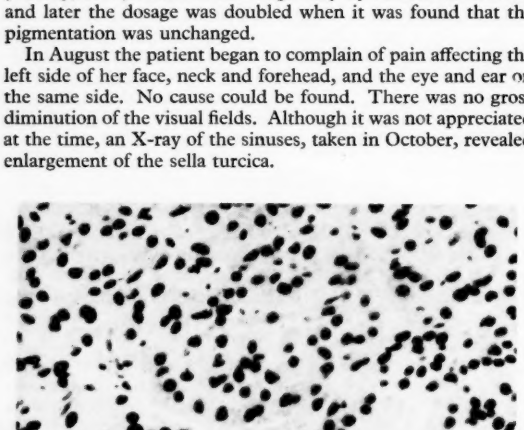

Fig. 1—Pituitary tumour from the first case showing anastomosing coils of cells which form palisades around the vessels. (Hæmatoxylin and eosin. × 300.)

Her symptoms persisted until Feb. 16, 1958, when severe pain and swelling were experienced in the left eye. A few hours later the patient started to vomit and became drowsy. On admission to hospital, on Feb. 18, she was semiconscious and uncooperative. Her temperature, pulse, and blood-pressure were normal. The left eye was proptosed and immobile, and showed signs of bleeding into the orbit. There was loss of sensation in the territory supplied by the left fifth cranial nerve. Both fundi appeared normal. Neck stiffness was present, and lumbar puncture revealed bloodstained cerebrospinal fluid.

The patient was treated by cooling, antibiotics, and œsophageal feeding. Nevertheless, she became deeply comatose, the pulse-rate rose, and signs of right-sided hemiplegia and Cheyne-Stokes breathing developed. She died three days after admission.

Necropsy

Pituitary.—Lying within and above the pituitary fossa there was a rounded hæmorrhagic tumour measuring 4×3×3 cm. The sella turcica was expanded to twice normal size, and its margins were eroded. The bulk of the growth lay above the sella, and the optic chiasm and nerves were stretched over its surface. On the left side the tumour infiltrated through the lateral wall of the sella, and extended forwards outside the dura to form an ill-defined firm mass, roughly 1 cm. in thickness, which terminated a short distance inside the optic foramen. The bone adjacent to the tumour did not appear to be infiltrated.

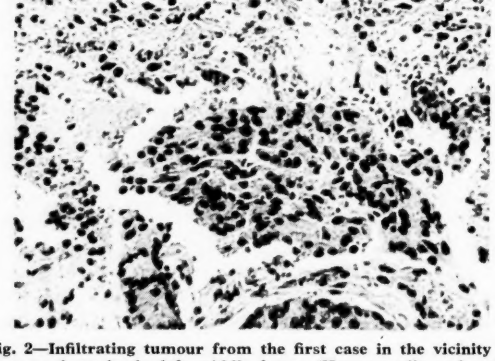

Fig. 2—Infiltrating tumour from the first case in the vicinity of nerve tissue in the left middle fossa. (Hæmatoxylin and eosin. × 220.)

There was slight diffuse hæmorrhage in the adjacent meninges. No identifiable pituitary tissue was seen.

Brain.—There was much compression and flattening of the third ventricle and related structures, while the lateral ventricles showed moderate flattening. Slight hæmorrhage had occurred into the brain substance at one or two points where it was in contact with the pituitary tumour.

The *left adrenal* remnant weighed 1·3 g. No adrenal tissue was noted on the right side. The *thyroid* was uniform in consistency and weighed 18 g.

Both *ovaries* were enlarged to about twice normal size and contained numerous small cysts, the largest being 3 mm. in diameter. There was an involuting corpus luteum in the left ovary.

Histology

Pituitary tumour.—There were large areas of hæmorrhage and necrosis. Where the growth was viable it was composed of short anastomosing columns of cells, which took up a palisade arrangement around the numerous capillary and sinusoidal blood-vessels in its substance (fig. 1). The cells had an abundant pale eosinophilic and finely granular cytoplasm with ill-defined margins. Their nuclei were compact oval or round, usually with a considerable chromatin content. The eosin-pyrol blue and periodic-acid Schiff trichome staining methods revealed scanty basophilic cytoplasmic granules in occasional

cells. The remainder were chromophobic. Where the tumour extended into the middle fossa, the cells became more pleomorphic and irregularly arranged, and infiltrated nerve tissue (fig. 2). At a few points they lay in sinusoidal vascular spaces. Thus the tumour was a transitional basophil carcinoma.

A segment of pars tuberalis was present in a section through the base of the infundibulum. It was composed of chromophobe cells showing no unusual features.

Left adrenal remnant.—The outer cortex was mildly nodular. A thin zona glomerulosa was present in many areas, and deep to this the cortical cells at times showed the disposition of the normal zona fasciculata. For the most part, however, the normal architecture of the inner cortex had been lost. Many of the cortical cells especially in this area were giant round forms, often with a pale finely vacuolated cytoplasm. In others, part or all of the cytoplasm was acidophilic and finely granular, or homogeneous and hyaline; in a few of these cells there was some orange-brown pigment. The nuclei of many of the giant cells were large and many were irregular and hyperchromatic. Abundant sudanophilic lipoid was present in all parts of the cortex.

Ovaries.—The cysts observed macroscopically were follicular. The majority showed a prominent theca interna in which luteinisation was often prominent. In places there was a conspicuous theca externa.

Skin.—The basal layer of the epidermis showed increased melanin pigmentation.

Sections of other tissues and organs showed no feature of note.

Hormone Assay of Tissues

The adrenal remnant (wet tissue) contained 1·72 μg. of 17-21-dihydroxysteroid per g. This is a very low level.

The pituitary tumour (freeze-dried) was analysed by bioassay for corticotrophin activity. Dr. M. P. Stack-Dunne reported as follows:

"Sayers assay (hypophysectomised rats, intravenous injection): potency 0·203 I.U. per mg.; fiducial limits ($P = 0·95$) 0·117–0·314. 42 rats were used in this assay, with three levels of the 2nd International Standard, and three levels of the test preparation. Tests for parallelism and linearity were satisfactory ($\lambda = 0·302$, $g = 0·1479$).

The tumour tissue was homogenised by hand in a modified 'Potter' homogeniser in 0·9% of sodium chloride containing 3 ml. per litre of glacial acetic acid, and allowed to stand about half an hour. It was then diluted with the same medium without filtering."

This figure (0·203 I.U. per mg.) is similar to that obtained from normal human pituitary tissue (Taylor et al. 1953). It indicates that the tumour contained at least 20 times as much corticotrophin as a normal gland.

The tumour was assayed roughly for melanophore expanding activity in toads by Prof. F. W. Landgrebe. It contained about 2 I.U. per mg., but, bearing in mind that the tissue had been stored a long time and that M.S.H. is the first hormone in pathological material to deteriorate, the figure is probably about that which would be obtained from normal pituitary tissue.

THE SECOND CASE

The patient (Montgomery and Welbourn 1957, case 11), a married woman of 34, was admitted to hospital in July, 1955. Eighteen months previously she had given birth to a premature stillborn child. Following delivery amenorrhœa persisted, her weight increased rapidly by 42 lb., she became hirsute, and she complained of progressive tiredness and muscular weakness.

Examination

She was obese, with a round red face and pronounced hirsutism of the moustache and beard areas. The limbs were thin and tapering in contrast to the obesity of the trunk and shoulders. There were no striæ. The blood-pressure varied from 145 105 to 180 120, but there were no other abnormal findings in the cardiovascular system.

Investigations

Chest radiography was normal, and there was no evidence of osteoporosis in the films of the spine. The skull film showed questionable enlargement of the sella turcica with some thinning of the posterior clinoid processes. Tomography of the adrenal glands, combined with insufflation of oxygen and intravenous pyelography, showed no apparent enlargement of the adrenals.

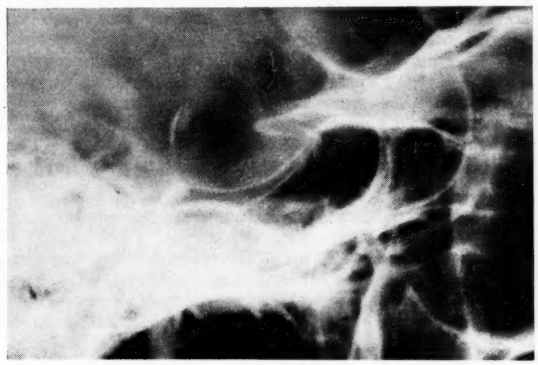

Fig. 3—Radiograph of pituitary fossa in the second case showing enlargement three years after operation.

The serum-electrolytes were normal, but the fasting blood-sugar level was 129 mg. per 100 ml., and the glucose-tolerance test showed a mild diabetic curve.

The urinary excretion of 17-ketosteroids varied between 10·9 mg. and 19·9 mg. per twenty-four hours, while the excretion of 17-hydroxycorticoids was nil per twenty-four hours in the resting state, and 22·2 mg. per twenty-four hours following stimulation with 25 mg. of corticotrophin (intravenously) in two successive days.

Treatment

Cushing's syndrome, probably as the result of adrenocortical hyperplasia, was diagnosed, and subtotal adrenalectomy was advised and carried out in two stages.

The left gland was explored on Aug. 9, 1955, and 90% of it was removed. Fourteen days later the whole of the right gland was excised. The weights of the resected portions were 9·0 g. and 2·6 g. respectively. Histological examination of the left gland showed hyperplasia, but the appearance of the right gland suggested nodular regeneration after extensive destruction in the past, possibly as the result of infarction.

Course

The patient recovered satisfactorily from both operations, and a good remission of the disease process was obtained. Postoperative cortisone replacement had to be continued indefinitely, for a trial withdrawal of the drug resulted in symptoms of adrenal insufficiency. Six months after adrenalectomy generalised pigmentation of the skin was noticed. It was first apparent some months earlier in the operation scars, but it gradually spread to involve the exposed parts of the body (see Montgomery and Welbourn 1957, fig. 180). A year after the operation a corticotrophin-stimulation test showed no detectable response of the adrenal remnant to exogenous corticotrophin.

During the next two years the patient's condition remained satisfactory on regular cortisone replacement, but the pigmentation never faded, even when the dose of cortisone was increased. In January, 1959, radiography of the pituitary fossa showed it to be enlarged with definite undercutting of the posterior clinoid processes (fig. 3), indicating a developing pituitary tumour. The visual fields and acuity, and the ophthalmological appearances were normal, however, suggesting that suprasellar extension of the tumour was unlikely.

Attempts were made by Professor Landgrebe to assay the patient's blood and urine for melanophore expanding activity. The material, however, was very toxic for toads, and no activity could be detected.

Second Operation

In view of the experience gained in the first case we considered that the lesion represented a direct threat to life and required removal. Accordingly hypophysectomy was advised

and carried out on Feb. 27, 1959. At operation the optic nerves and chiasma were found to be much elevated over a pituitary tumour, the supradiaphragmatic portion of which projected upwards for about three-quarters of an inch. After the removal of 5 ml. of yellow cystic fluid the solid intracapsular portion of the tumour was removed with curettes, and the supradiaphragmatic portion of the capsule was then excised. Finally yttrium-90 in wax was inserted into the pituitary fossa in order to obtain total destruction of any remaining pituitary tissue.

Progress

Following operation the patient remained confused for several days, and on the sixth day she had a brief attack of twitching of the muscles round the mouth. There was temporary weakness of the left sixth cranial nerve for a few days, but recovery was complete. During the immediate preoperative and postoperative phases additional cortisone was given to cover the stress of the operation. Mild diabetes insipidus developed on the tenth postoperative day, and was easily controlled with daily intramuscular injections of 1 ml. of 'Pitressin' tannate in oil.

One month after the operation the patient left hospital fully ambulant and feeling well, and taking 0·2 mg. of thyroxine each day in addition to the daily dose of 37·5 mg. cortisone acetate. Progress since leaving hospital has been satisfactory. Six months after operation the pigmentation had gone, but the diabetes insipidus still required treatment with 0·5 ml. of pitressin tannate in oil daily.

Histology

Tissue from the wall of the cyst showed the presence of anterior pituitary tissue. This was largely composed of eosinophil cells with a few scattered basophils. These basophil cells showed no hyalinisation (Crook's) but did show vacuolisation similar to that seen in castrate glands.

Pituitary tumour.—Several fragments of tumour were examined. The tumour cells were somewhat larger than those of the normal anterior lobe. They showed some tendency to form acini lined by cubical to columnar cells, with nuclei at their bases, so that the tissue had an adenoid appearance. Granule stains showed that many cells were chromophobic, but that some were granular. It was impossible to decide whether or not the tumour was maglignant, but its histological structure was identical with that of the first case which was locally invasive. It is best described as a transitional basophil adenoma.

Discussion

It seems likely that in each patient there was a small adenoma of the pituitary which continued to grow after adrenalectomy. The generalised pigmentation, which was such a striking feature of both our patients and also of several of those reported previously, was probably caused by melanocyte-stimulating hormone secreted by the tumour, although we were unable to obtain direct evidence of this. We have often seen pigmentation in the operation scars of patients who have undergone adrenalectomy for Cushing's syndrome, but in other cases it has faded with the passage of time.

It is hard to understand the complete absence of adrenal steroids from the urine two months before death and the inactive appearance of the adrenal remnant after death in the first case.

There were no clinical or other laboratory features of adrenal insufficiency and the tumour contained a large amount of corticotrophin.

Time alone will show the proportion of patients in whom pituitary tumours will become manifest after adrenalectomy. Possibly in the future we shall have to consider hypophysectomy as an alternative to adrenalectomy more often than we do at present. In the meantime we think it wise to take X-rays of the pituitary fossa at regular intervals after operation, and to regard seriously widespread pigmentation which does not fade rapidly under treatment with cortisone.

Summary

A girl of 15 and a woman of 34, with Cushing's syndrome, responded well to subtotal adrenalectomy. Subsequently they became deeply pigmented, and showed radiographic evidence of pituitary-fossa enlargement. Three years after operation the first died from the local effects of a transitional-basophil carcinoma of the pituitary, and the second had an adenoma of similar histological structure removed surgically.

We are grateful to Dr. J. A. Smyth for referring the first patient to us; to Mr. D. W. Neill for the biochemical investigations and for the translation of the paper by Siebenmann; to Dr. D. C. Porter, Dr. W. H. T. Shepherd, Dr. J. O. Y. Cole, and their staff for the radiological reports; to Prof. J. H. Biggart for the histological report in the second case and for his advice; to Prof. L. W. Landgrebe and Dr. G. M. Mitchell, of the Welsh National School of Medicine, for the estimation of melanophore-expanding substance or hormone; to Dr. M. P. Stack-Dunne, of the National Institute for Medical Research, Mill Hill, London, for the assay of corticotrophin; and to Mr. D. Mehaffey and Mr. R. G. Wood for the photographs.

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ANALGESIA FOR BURNS DRESSINGS

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THE dressing of extensive burns without anæsthesia can cause considerable pain and distress. General anæsthesia, given frequently, carries an appreciable risk in the severely burned patient and interferes with nutrition. Ideally, one requires a potent analgesic which is safe to use repeatedly, and which does not so far sedate the patient that he cannot cooperate during the dressing or eat his meals at the proper time.

Previous attempts have been made in this unit to find such a drug. Morphine and 'Omnopon' have been used, as for preoperative medication, and a trichlorethylene inhaler as in obstetric practice. The two drugs were inadequate; and though trichlorethylene was effective with a cooperative patient, it was difficult to administer to children.

Recent reports on " ataralgesia "—i.e., a state of calmness and freedom from pain (Hayward-Butt 1957, 1958, Goosen 1958, Mitchell and Minor 1958, Smith et al. 1958)—and on the use of analgesics in large doses (Christie et al. 1958, Gershon et al. 1958) suggested that effective analgesia might now be possible.

Methods

39 patients were observed on 107 occasions during a dressing following the administration of an analgesic. 34 had burns involving 10–62% of the body surface; the other 5 were patients with smaller burns who had complained of pain at a previous dressing. An objective assessment of the patient's reaction to the dressing was made by the same observer. The reaction was graded as − for no sign of any discomfort, ± for a frown or slight movement on one occasion suggesting a little discomfort, + for more definite indication of pain but without distress, and up to ++++ for persistent crying or complaint. In adults a subjective assessment of pain was also obtained where possible.

10 patients had dressings done with and without analgesia and thereafter were given the option of it. Side-effects, such as nausea and vomiting, and failure to take normal meals, were noted. The respiration-rate, counted for one minute, was recorded in nearly all cases.

Pethidine hydrochloride was used as the analgesic (Hayward-Butt 1957) the dosage being adjusted individually. Amiphenazole (' Daptazole ') was dissolved in the pethidine solution to counteract respiratory depression (about 30 mg. for each 75 mg. pethidine). Tranquillisers were also used. Mepazine (' Pacatal ') was given intramuscularly in doses ranging from 150 mg. at 8 years to 300 mg. for a man, and by mouth in doses ranging from 50 mg. at 4 years to 250 mg. for a man; and on 4 occasions perphenazine (' Fentazin ', 4–8 mg. by mouth at 4–6 years).

The methods of administration were:

(*a*) Pacatal intramuscularly and pethidine-amiphenazole intramuscularly on 7 occasions in 4 patients (aged 8–30).

(*b*) Tranquilliser by mouth and pethidine-amiphenazole intramuscularly on 22 occasions in 13 patients (aged 4–34).

(*c*) Tranquilliser by mouth and pethidine-amiphenazole intravenously on 6 occasions in 3 patients (aged 6–22).

(*d*) Pethidine-amiphenazole intramuscularly only on 41 occasions in 23 patients (aged 4–48).

(*e*) Pethidine-amiphenazole intravenously only on 31 occasions in 15 patients (aged 4–70).

Results

No method was uniformly successful. In general the results were much better in adults than in children, but there was considerable individual variation.

Effective analgesia (−, ±, or + reaction) was obtained with intravenous pethidine-amiphenazole on 25 out of 31 occasions—a higher proportion than with any other method (table I).

The addition of a tranquilliser by mouth did not increase the analgesic effectiveness of pethidine-amiphenazole intramuscularly: 9 patients had methods (*b*) and (*d*) on different occasions with no appreciable difference in the results. Intramuscular pethidine was effective on 15 out of 41 occasions (37%) compared with 8 out of 22 (36%) when an oral tranquilliser was also used. Intramuscular pacatal was more effective, but the side-effects made its routine use seem unjustified.

TABLE I—DEGREE OF " PAIN " REACTION FOLLOWING ANALGESIA

—	Effective			Little effect	Ineffective		Total
	−	±	+	++	+++	++++	
(*a*) Pacatal I.M. Pethidine I.M.	..	1	2	3	1	..	7
(*b*) Tranquilliser by mouth Pethidine I.M.	..	1	7	4	8	2	22
(*c*) Tranquilliser by mouth Pethidine I.V.	..	..	1	..	5	..	6
(*d*) Pethidine I.M.	3	4	8	15	7	4	41
(*e*) Pethidine I.V.	5	10	10	2	3	1	31

I.M. = intramuscularly. I.V. = intravenously.

TABLE II—SIDE-EFFECTS FROM ANALGESIA

—	Occasions used	Vomiting	Nausea (without vomiting)	Omission of meal	Drowsiness	Respirations less than 18 per min.
(*a*) Pacatal I.M. Pethidine I.M.	7	..	..	3	6	1
(*b*) Tranquilliser by mouth Pethidine I.M.	22	7	4	2	12	..
(*c*) Tranquilliser by mouth Pethidine I.V.	6	1	2	..	2	..
(*d*) Pethidine I.M. ..	41	5	3	4	17	1
(*e*) Pethidine I.V. ..	31	1	3	..	21	9

Side-effects

Respiratory depression, to a rate below 18 per minute, was noted on 11 occasions, usually following the intravenous administration of pethidine (table II). On one occasion the rate fell below 12 per minute (to 8 per minute) in a woman on sedation for epilepsy, but it increased to 20 within ten minutes. The depth of respiration always increased when the rate decreased, and cyanosis did not occur.

Drowsiness was frequent (58 occasions), especially when enough analgesic was given to produce a good effect. It was apparent most often after pacatal intramuscularly with pethidine intramuscularly (6 out of 7 occasions); and on 3 occasions it prevented the patient having the next meal. Although drowsiness commonly accompanied intravenous pethidine, it usually disappeared before the patient left the dressing-room, and never interfered with meals. Drowsiness after intramuscular pethidine lasted longer.

Nausea and vomiting caused more complaint from the patient than other side-effects. In spite of the claimed antiemetic action of pacatal, nausea and vomiting occurred on 54% of occasions when it was given by mouth—i.e., more often than when pethidine alone was given intramuscularly (20%) or intravenously (13%).

Pacatal for injection is an irritant solution of fairly large volume (the adult dose of 300 mg. is contained in 12 ml.). Moreover, because of the extent and distribution of the burns, we could not always give the intramuscular injection as deeply as is desirable. As a result, 1 patient developed a sterile abscess from it, and the 2 children complained of pain for several hours at the site of injection.

Dosage of Pethidine

Effective analgesia was obtained only with large dosage and was almost always accompanied by slight drowsiness. If inadequate on the first occasion for an individual patient the dose was increased to try to obtain an analgesic level.

Intravenously, the " effective " dose for children (4–14 years) was 100–150 mg.; and for those over 14 years, 150–250 mg. Using these dosages, a −, ± or + " pain " reaction was obtained on 5 out of 10 occasions in children, and on 18 out of 21 occasions in those over 14 (table III). The failures in those over 14 obtained adequate analgesia when the dose was increased for subsequent dressings. Of the 3 patients who had a good effect from lower dosage, 2 were epileptics on routine sedation and the 3rd had only a small residual raw area after an extensive burn.

Intramuscular pethidine was less certain in its action. The dosage generally used was 100–150 mg. at 4–7 years, 150–200 mg. at 8–14 years, 200–250 mg. for females over 14 years,

TABLE III—DEGREE OF "PAIN" REACTION IN RELATION TO DOSAGE OF PETHIDINE

Intravenous

Age (yr.)	Dose (mg.)	Effective			Little effect	Ineffective		Total
		−	±	+	++	+++	++++	
4–14	50	..	..	..	..	2	..	2
	100–150	1	2	2	2	2	1	10
Over 14	75–125	1	1	1	..	1	..	4
	150–250	3	7	8	..	3	..	21
Total low dose		3			..	3		6
Total high dose		23			2	6		31

Intramuscular

Age (yr.)	Dose (mg.)	Effective			Little effect	Ineffective		Total
		−	±	+	++	+++	++++	
4–7	50–75	..	..	..	1	3	1	5
	100–150	..	1	2	5	6	4	18
8–14	100	..	..	..	..	2	..	2
	150–200	1	2	7	9	4	1	24
Over 14	150	..	..	2	1	1	..	4
	200–300	2	3	6	6	..	..	17
Total low dose		2			2	7		11
Total high dose		24			20	15		59

and 200–300 mg. for males over 14. This dosage was "effective" (−, ±, or + reaction) on 11 out of 17 occasions in adults, and 13 out of 42 occasions in children (table III). Smaller quantities than these were usually inadequate.

Patients' Choice

10 patients were given the option of having analgesia, after having had dressings done with and without it. 8 patients requested analgesia; the other 2 declined because of side-effects (one dizziness, the other nausea and vomiting).

5 other patients had analgesia for their first dressing and requested it for future occasions, although in 2 cases the analgesia was not graded as "effective" by the observer. In 2 of these a later dressing was attempted without analgesia, but had to be postponed until the injection was given.

Discussion

The pain felt by a patient is difficult to grade. Burns with partial skin loss are painful at the time of injury and become less so as healing proceeds. Burns with whole skin loss are insensitive at first, but become painful as the slough separates, leaving a raw area exposed. Burns involving the hands appeared much more painful than those of the back. The use of a cream dressing was less troublesome than one which became adherent. The amount of pain would be different between patients and between different dressings on the same patient. In our opinion, however, all the dressings observed would have given considerable discomfort if done without analgesia.

The individual reaction to pain varies considerably, and this variation has to be taken into account when trying to reduce as much as possible the upset caused by treatment. Some patients are fearful of any unfamiliar procedure, while others only become so by previous unpleasant experience. The more the unpleasant experience is repeated, the harder it is to eradicate the fear. This situation is more obvious in children, in whom the degree of reaction to a dressing is not necessarily related to the painful stimulus.

In this study no attempt was made to distinguish between response to pain or fear alone in grading the reactions. We noticed that young children (4–6 years) tended to be upset by side-effects of a drug; whereas teenagers usually accepted them as proof that the drug was effective.

We hoped that a tranquilliser and an analgesic, given together, might remove the fear as well as the pain of dressings, and by their repeated use build up an experience which was not unpleasant. This hope was not fulfilled. The tranquillising effect was not obvious, and the patient was often upset by the side-effects.

It is not clear why pacatal, given by mouth, increased the incidence of nausea and vomiting. Perhaps, in the extensively burned, it acts as a gastric irritant before absorption. Certainly when given intramuscularly it acted as a local irritant, but did not cause nausea or vomiting.

In some patients, repeated use of analgesia alone decreased the fear of dressings.

Compared with the intramuscular route, intravenous injection ensured that the effect more closely corresponded to the duration of the dressing. It also allowed adjustment of dosage, since with slow injection of the drug the onset of slight drowsiness usually indicated adequate analgesia. Unfortunately venepuncture itself may be difficult in the extensively burned, and especially in children. An important finding is that, to be helpful, the drugs used must be given in high doses. For example, a woman aged 22 with a 25% burn got little relief from 100 mg. pethidine intravenously. Increasing the dose to 150 mg. brought little improvement, and only when 200 mg. was given was analgesia obtained.

The safety of medication is important. Although respiration was depressed in some cases, this never caused concern and no other immediate ill effects were noted. Pethidine is recognised as a drug of addiction, and tolerance to it may be developed. In 2 patients in this series, who had had pethidine on 4 and 6 occasions, it was felt that the same dose was beginning to have less effect. Another patient said she enjoyed the feeling produced by the drug—a situation which could lead to addiction if she had access to it. Unfortunately no powerful analgesic is free of these disadvantages.

All but 1 of the 13 adults, over 20 years of age, said they appreciated the analgesia, and felt that dressings were easier because of it, although not always pain-free. This failure to abolish pain completely meant that younger people often continued to complain, although most teenagers, after several dressings, would ask for their injection. The young children (4–6 years) were the most difficult to assess. Although sometimes one had the impression that crying was unrelated to pain, only with intravenous medication to the stage of drowsiness did one appreciably reduce the disturbance to the patient.

Summary

39 patients were observed during 107 burns dressings following the administration of an analgesic.

Combinations of a tranquilliser (intramuscularly or by mouth) with pethidine-amiphenazole intramuscularly or intravenously were tried.

Pethidine-amiphenazole alone, given intravenously, gave the best results. The effective dosage of pethidine

was 100–150 mg. at ages 4–14, and 150–250 mg. for older patients.

This type of analgesia was acceptable and effective in adults, but appeared much less effective in young children.

I wish to thank Mr. D. MacG. Jackson for his cooperation and permission to study patients under his care; Dr. L. J. Wolfson for advice on the drugs used; and Dr. J. P. Bull for helpful criticism in the preparation of this paper. I am grateful to the nursing staff for their cooperation, and to the patients themselves for their comments on the effect of the methods used.

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PNEUMOCYSTIS CARINII PNEUMONIA ASSOCIATED WITH HYPOGAMMAGLOBULINÆMIA

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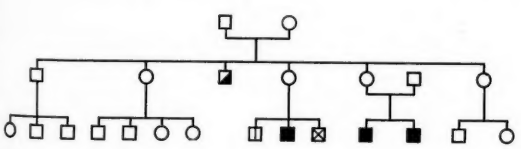
Pneumocystis carinii pneumonia of infancy is a fairly common disease on the continent of Europe, where it affects chiefly weakly and immature babies, and where it is associated with a normal electrophoretic pattern of plasma-proteins (Ahvenainen 1957). In this country, however, the infection is uncommon, and the first cases were reported by Baar (1955), Hutchison (1955a, 1955b), and Bird and Thomson (1957). Bird and Thomson commented that their two cases were older than those usually seen on the Continent, and they noted that of the four Scottish cases at least two had low gamma-globulin levels. Very similar was the case from the South-Western United States recorded by Eberling and Cohen (1958), where the baby was 6 months old and the gamma-globulin concentration was low. We report here a further example of this association.

Case-report

A boy of $9^1/_2$ months was admitted to the Royal Aberdeen Hospital for Sick Children on Nov. 14, 1957. His mother was Danish and his father Scottish. A male cousin on the maternal side died at the age of 4 months from generalised sepsis. As he died 9 years ago, plasma-protein studies were not carried out, but it seems likely that this child suffered from hypogammaglobulinæmia, and we are indebted to Dr. O. Bouet, of Brørup, Denmark, for the information that the child was admitted to hospital at the age of 2 months and died there aged $4^1/_2$ months following pyogenic skin and lung infections



■ Affected males.
⊠ Unaffected male (plasma-gamma-globulin 0·79 g. per 100 ml.).
◫ Died at age of 16 hours.
◪ Died aged 25 years from cerebral tumour.
□ Male, alive and well (no plasma-protein studies).

Fig. 1—Family tree.

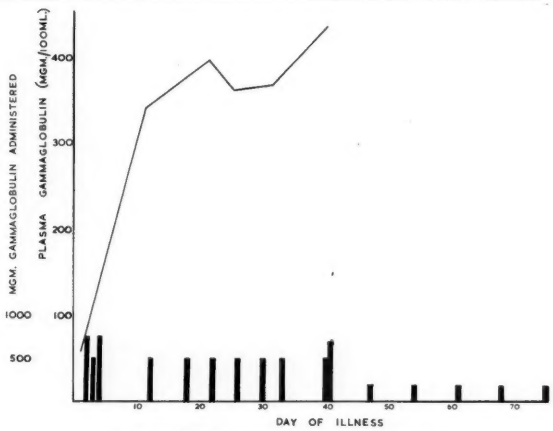


Fig. 2—Administration of gamma-globulin.

accompanied by diarrhœa. Blood-counts were normal. Prof. P. Plum, of Copenhagen, has carried out preliminary studies on a 14-month-old brother of this child, showing the serum gamma-globulin to be 0·79 g. per 100 ml., estimated by electrophoresis. The case of our patient's brother (fig. 1) who died from generalised vaccinia, has been described by Galloway and MacBean (1956, 1958).

Our patient was born by spontaneous vertex delivery, weighed 8 lb. 1 oz., was breast-fed for 8 weeks, and, apart from intermittent diarrhœa, progressed normally until 3 weeks before admission to hospital. Stool-culture at home showed no pathogens. His illness began with listlessness, irritability, and dry cough. Acute tonsillitis was diagnosed but his symptoms did not settle after a course of sulphonamide, and he became increasingly tired and later breathless on exertion, with slight cyanosis of his finger nails when he cried. During those 3 weeks he was anorexic, losing about 1 lb. in weight.

He was an extremely fretful, ill-looking boy of 18 lb., who showed evidence of weight loss. His lips and extremities were cyanosed when he cried, and he had early clubbing of fingers and toes. His pulse-rate was 156 and respiratory-rate 48. His rectal temperature was 98·6°F, and throughout the whole illness it was seldom raised. The air entry was diminished over the middle zones of the right chest, but there were no adventitious sounds, and the percussion note was unimpaired. Examination was otherwise negative; the spleen was not palpable; no superficial lymph-nodes could be felt, and there was no other evidence of infection. There were no abnormal findings in the urine; chest X-ray showed extensive opacities in both lungs with partial collapse of the right lower lobe.

In view of the family history, plasma-proteins were estimated on the morning following admission. Total protein (by specific gravity) was 5·7 g. per 100 ml., and by paper electrophoresis (using an 'EEL' scanner) the components were: albumin 55%, α_1-globulin 5%, α_2-globulin 19%, β-globulin 20% and γ-globulin 1%. Between Nov. 16 and 18, 2000 mg. of gamma-globulin was administered (fig. 2), and confirmation of the low serum level was obtained by examination of a sample of blood sent on Nov. 26 to the Medical Research Council working party on hypogammaglobulinæmia. In the sample gamma-globulin estimation by free electrophoresis was 190 mg. per 100 ml., and by precipitin-diffusion method was 40 mg. per 100 ml. Maternal and paternal plasma-protein electrophoresis was normal. The child's blood-group was A, Rh (D) positive, the serum containing no normal isoagglutinins. A blood-count showed Hb 80%; W.B.C. 21,600 per c.mm., neutrophils 77%, eosinophils 1%, lymphocytes 18%, and monocytes 4%; platelets 580,000 per c.mm.; repeat blood-counts were similar. Several throat and cough swabs were taken, the initial one giving a growth of *Streptococcus viridans* only, and later swabs giving similar results or being sterile on culture, apart from one on Dec. 20 which grew *Staphylococcus*

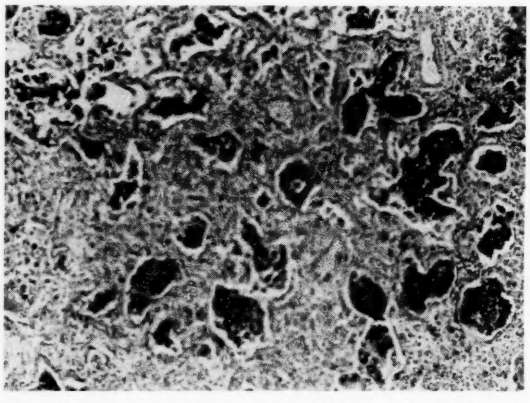


Fig. 3—Acellular masses in the alveoli. (Periodic acid-Schiff. × 108.)

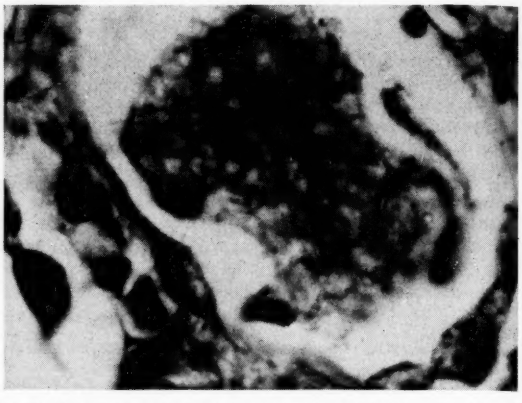


Fig. 4—Detail of the "ovoid bodies". (Heidenhein's azan. × 1500.)

aureus. Mantoux test was negative at a dilution of 1 in 1000. Stool trypsin was present in normal amount.

The boy's progress was steadily downhill. 2 days after admission he had to be started on oxygen therapy, and he required this continuously and in increasing concentration for $2^1/_2$ months until he died on Jan. 28, 1958. This difficulty in maintaining adequate oxygenation was one of the most striking features of the illness. Courses of penicillin, streptomycin, tetracycline, erythromycin, and novobiocin had no effect on the course of the illness, nor did prednisolone, which was given for 3 weeks in decreasing dosage commencing with 15 mg. daily, produce any change. Following inclusion of the case in the Medical Research Council clinical trials, gammaglobulin dosage was regulated to conform to that series. The lung signs varied greatly, widespread crepitations being present at times, while at other periods no adventitious sounds could be heard. Feeding became difficult and terminally he had intractable diarrhœa.

Necropsy

Necropsy was performed some 16 hours after death. The child showed the appearances of wasting with slight protuberance of the abdomen. No superficial lymph-nodes were palpable, and the virtual absence of lymph-nodes was confirmed when the body was opened.

The main findings were in the lungs which were firm, fleshy, and fairly uniformly solid, apart from some aeration of the anterior fringe of the right middle lobe. They were pale pink with scattered whitish areas throughout, and were unusually dry. The appearances suggested carnification, but there was no distortion of the bronchial tree, and no evidence of pus either in the trachea or bronchi. A little dark serous fluid could be expressed from the major bronchi into the trachea, but the trachea itself contained no exudate. The pleural surfaces showed slight puckering but there was no pleural reaction.

Culture of the lung tissue produced a scanty growth of *Staph. aureus* (coagulase positive) and, on enrichment, *Str. fæcalis*. The other organs were normal.

Histological Findings

In the lungs there is a varied picture, but in all areas examined there is evidence of an interstitial pneumonia—the alveolar septa being thickened and infiltrated by lymphocytes and large mononuclear cells. Plasma-cells are conspicuous by their absence. In some areas there is good aeration, and the alveoli contain only scattered macrophages, red cells, and desquamated alveolar cells. In others the alveoli and alveolar ducts are distended and contain a slightly eosinophilic honeycombed exudate, and the air sacs themselves are lined by cuboidal epithelium. The exudate is strongly positive to periodic acid-Schiff (P.A.S.) staining and is relatively acellular, but scattered alveolar macrophages containing P.A.S.-positive material can be identified.

Staining with Giemsa, Heidenhein's azan stain, McManus-Hotchkiss, and phloxin-tartrazine shows that the exudate consists of collections of small round or ovoid bodies in which granules of chromatin can be occasionally identified (figs. 3 and 4). There is no evidence of inclusion-body disease. Smears of the lung tissue, unfortunately, were not made.

Histology from the other organs reveals no notable abnormality apart from a generalised lack of plasma-cells. One lymph-node examined appears normal, though of small dimensions, and the liver shows scattered areas of centrilobular fatty change.

Sections of the lung were sent to Prof. H. Hamperl, of Bonn, who agreed that the changes were pathognomonic of pneumocystis pneumonia.

Discussion

The clinical picture of pneumocystis pneumonia is clearly defined, and this diagnosis should be considered in any infant with pneumonia showing the characteristic features of increasing oxygen starvation, failure to respond to antibiotics, and radiological changes out of proportion to the clinical signs. It is furthermore necessary to investigate the serum-protein pattern in these cases.

The case here described throws no further light on the ætiological agent in pneumocystis pneumonia, but supports the association noted by Bird and Thomson (1957) between this disease and hypogammaglobulinæmia. As in their cases, this patient also did not have the recurrent pyogenic infections usually seen in hypogammaglobulinæmia. The occurrence of diarrhœa in patients with congenital hypogammaglobulinæmia has recently been emphasised by Firkin and Blackburn (1958), and was a prominent feature in our case.

We are indebted to Prof. John Craig and Prof. J. S. Young for their advice and criticism, and to Mr. William Topp for the photographs.

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Addendum

Since this paper was written a further male child has been born into the family (fig. 1). This third child has now died and Dr. Philip Evans has kindly permitted us to state that the boy was admitted to The Hospital for

Sick Children, Great Ormond Street, where he died at the age of $7\frac{1}{2}$ months from *Pneumocystis carinii* pneumonia accompanying congenital hypogammaglobulinæmia. Histological examination of the lungs has confirmed the clinical diagnosis. Thus, of the three boys in the family, all have suffered from congenital hypogammaglobulinæmia, one has died from generalised vaccinia, and two from *Pneumocystis carinii* pneumonia.

Preliminary Communication

FACIAL FLUSHING PRODUCED IN PATIENTS WITH CARCINOID SYNDROME BY INTRAVENOUS ADRENALINE AND NORADRENALINE

PATIENTS with metastatic carcinoid tumours may exhibit episodic facial flushing, diarrhœa, asthmatic attacks, and cardiac valvular lesions. Abnormally high levels of 5-hydroxytryptamine (5-H.T.) are found in the blood in this syndrome, with large quantities of the 5-H.T. metabolite, 5-hydroxyindole acetic acid (5-H.I.A.A.) in the urine. The various features of the syndrome are seen usually only when there exist metastatic deposits drained

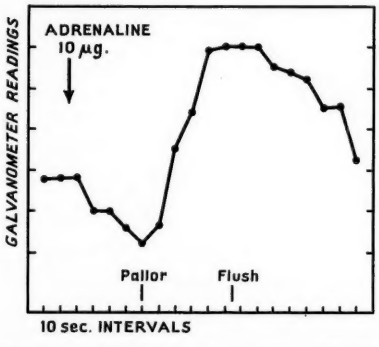

Fig. 1—Changes in forehead skin-temperature following 10 μg. of adrenaline intravenously.

by veins outside the portal system, and it has been considered likely that the flushing attacks are due to the release of gushes of 5-H.T. directly into the systemic venous system. Release of 5-H.T. into the portal venous system, by contrast, would expose the 5-H.T. to early destruction by mono-amine oxidase in the liver. However, no convincing rise in either total or free (i.e., not platelet-bound) 5-H.T. has yet been demonstrated in the blood during a flush.

We describe here the provocation of typical flushes in patients with the carcinoid syndrome by means of small intravenous doses of adrenaline or noradrenaline.

Six patients with the carcinoid syndrome were studied. The experimental nature of the present investigations had been explained to all of them, and all were volunteers. In three instances (to be mentioned later) the administration of adrenaline was followed by transient abdominal pain; on one occasion only was this other than mild. The remaining procedures were not associated with unpleasant symptoms. All the patients had histologically proven carcinoid tumours and all had an abnormally high urinary 5-H.I.A.A. output. All except one had experienced spontaneous flushes; the exception was a man who was known to have hepatic metastases.[1] It was found in all six patients that the intravenous administration of adrenaline or noradrenaline in the dose range 2–20 μg. was followed by an apparently typical carcinoid flush after an interval varying from 40 to 120 seconds; the longer intervals occurred in patients with cardiac lesions. Adrenaline appeared the more potent of the two drugs, usually being effective at 50–60% of the dose of noradrenaline in a given subject. Fig. 1 shows the effect of 10 μg. of adrenaline administered to one patient. Skin-temperature changes on the forehead were followed by means of a thermistor recording on a galvanometer scale. Following the injection, an initial pallor appeared, to be overcome by the succeeding flush. The man in whom this record was obtained was of particular interest in that he had had no spontaneous flushes. Flushes were, however, provoked by both adrenaline and noradrenaline.

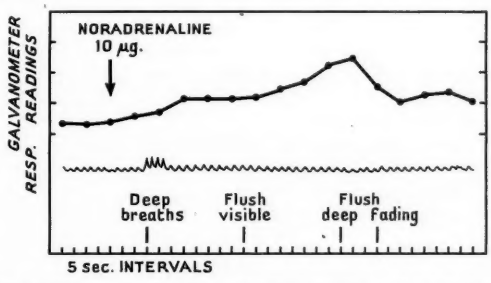

Fig. 2—Changes in forehead skin-temperature and stethograph record following 10 μg. of noradrenaline intravenously.

During the present studies, Schneckloth et al.[2] reported that intravenous noradrenaline provoked flushes in the carcinoid syndrome. They found in two patients that several hypotensive agents caused flushes, and, observing a hypotensive swing after the initial pressor response to noradrenaline, they appear to have concluded (see also Page [3]) that hypotension was the cause of the noradrenaline-provoked flush. However, we have observed flushes following noradrenaline when there has been no period

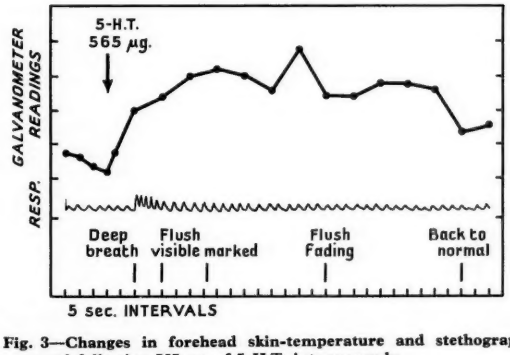

Fig. 3—Changes in forehead skin-temperature and stethograph record following 565 μg. of 5-H.T. intravenously.

of hypotension. Alternatively, if the rise in arterial pressure precipitates the flush, the mechanism must be extremely sensitive, since we have induced flushes with doses of noradrenaline and adrenaline which had only slight pressor effects.

1. Keen, H. *Diabetes*, 1959, **8**, 392.
2. Schneckloth, R. E., Page, I. H., Del Greco, F., Corcoran, A. C. *Circulation*, 1957, **16**, 523.
3. Page, I. H. *Physiol. Rev.* 1958, **38**, 277.

Four patients of the present series had diarrhœa. Intravenous adrenaline, in addition to causing flushes, was followed by abdominal pain and increased peristalsis in three of these. We have not observed this effect following noradrenaline.

In no instance has the induced flush been associated with headache or hypotension, which might be expected if a comparable flush were due to the release of histamine into the general circulation.

No effect has been observed following intravenous tyramine hydrochloride in doses up to 200 μg., or following ephedrine hydrochloride, amphetamine sulphate, or methylamphetamine hydrochloride in doses up to 50 μg. The response to noradrenaline can be abolished by oral dibenyline.

Simultaneous flush and respiratory records were made in one patient, the tracings of respiratory rate and depth being obtained with a simple stethograph.[4] Fig. 2 shows the effect on respiration and the course of the flush following the intravenous injection of 10 μg. of noradrenaline. 12 seconds after the intravenous dose four deep respirations are seen, the flush starting about 60 seconds after the injection. Fig. 3 shows the sequence of events after the intravenous injection of 1·3 mg. of 5-H.T. creatinine sulphate (=565 μg. 5-H.T. base) to the same patient. 5-H.T. causes overbreathing similar to that following noradrenaline, but in this instance the flush occurs almost at once.

Adrenaline, noradrenaline, and 5-H.T. all stimulate respiration.[3 5] We have repeatedly observed, however that, whereas adrenaline and noradrenaline will provoke moderate hyperpnœa followed by a severe flush, intravenous 5-H.T. in the same patient, whilst causing very much more pronounced overbreathing than will adrenaline or noradrenaline, is followed by a milder flush. This observation has important implications. The time relationships of flushes following intravenous adrenaline and noradrenaline suggest that these drugs cause the release of some substance, probably from the tumour tissue, into the general circulation. If the released substance were 5-H.T., a second bout of respiratory overactivity might be expected at the start of the flush. Indeed, considering the depth of the flush following adrenaline or noradrenaline, the second episode of increased respiration should be more striking than the first. However, on no occasion have we observed a convincing second episode of overbreathing in the course of a provoked flush. Further, we have not seen respiratory gasps at the onset of spontaneous flushes in these patients, though Schneckloth et al.[6] have described a case in which overbreathing was seen at the onset of spontaneous flushes, and Thorson [7 8] has observed hyperpnœa at the height of the flush in several patients.

In one patient, the right common carotid artery was punctured under local anæsthesia and the effect of intracarotid administration of noradrenaline studied. With an intracarotid dose of 4 μg., pronounced unilateral facial pallor was seen at once, but there was no subsequent flush. When 16 μg. of noradrenaline was injected by this route, generalised facial flushing occurred after 60 seconds. The flush was simultaneous in onset on the two sides, but was slightly masked on the right by persisting pallor.

This experiment excludes the possibility of the induced flush being due to an altered responsiveness of the skin vessels to noradrenaline, and suggests that adrenaline and noradrenaline cause flushes in patients with the carcinoid syndrome by releasing from a central site—probably tumour tissue—a substance which, directly or indirectly, dilates the blood-vessels of the skin, antagonising and overcoming the cutaneous vasoconstriction which is the normal local effect of adrenaline and noradrenaline.

The possibility of this effect being a nervous reflex peculiar to patients with the carcinoid syndrome has not been completely excluded, but is, we feel, unlikely.

Samples were obtained by catheter from the hepatic vein and from the upper inferior vena cava of one patient during deep flushes provoked by noradrenaline. Free plasma-5-H.T. was assayed biologically by the method of Vane.[9] No change in the free plasma-5-H.T. level was demonstrable during the flushes. In the same patient 5-H.T., sufficient to cause only a mild facial flush when injected into a hand vein, was easily detected in samples from the superior vena cava. It seems, therefore, that 5-H.T. is not the humoral substance responsible for the induced flushes. This problem is being investigated further.

SUMMARY

In each of six patients with the carcinoid syndrome small intravenous doses of adrenaline or noradrenaline caused flushes indistinguishable clinically from the spontaneous flushes of the carcinoid syndrome.

In one case no spontaneous flushes have occurred before or since the induced flushes.

In three cases, the administration of adrenaline was followed by abdominal pain and hyperperistalsis.

The available evidence suggests that the induced flushes are due to the release of a vasoactive substance from a central site. This substance does not appear to be 5-H.T.

We are grateful to all these patients for their willing cooperation, and in particular we are indebted to H. B., on whom the most extensive tests have been performed. We also wish to thank Dr. J. W. Litchfield, Dr. E. Idris Jones, Dr. P. B. S. Fowler, Mr. A. M. Desmond, and Mr. E. A. Crook for permission to study patients under their care; Dr. M. Sandler for introducing us to two of these cases and for a number of the 5-H.I.A.A. estimations; and Dr. J. F. Mowbray for very considerable help with the various forms of recording apparatus. The 5-H.T. creatinine sulphate was given by Sandoz Limited.

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6. Schneckloth, R. E., Page, I. H., Corcoran, A. C. *Circulation*, 1959, **19**, 766.
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"... A brilliant idea for an experiment is one that works out successfully; a silly idea is one that doesn't work out. Both may sound equally nonsensical when first proposed. A Sunday morning experiment is one that the investigator is ashamed to try out except on Sunday morning when everybody else is absent from the laboratory and can't make fun of him."—HAROLD L. STEWART, *Cancer Res.* September, 1959, p. 804.

New Inventions

NEW METHOD FOR SECURING DRESSING-DRUM LININGS

CYLINDRICAL dressing-drums have a number of serious disadvantages, and there are more suitable ways of packing surgical goods for steam sterilisation than in these containers. For some time to come, however, these drums will remain in use in many hospitals, and the modification described here has been made in an attempt to overcome one of their disadvantages.

Fig. 1—Drum with usual type of lining unfolded. This will introduce contamination.

It is important that dressing-drums should be lined, in order to prevent recontamination of their load.[1] In many hospitals, however, in drums opened by a pedal-operated arm, no lining is used. The reasons for not using a lining are that if the lining were folded back out of the way of the user it might touch the outside of the drum and become contaminated; or, if the lining were disturbed by each user, it would fall back on to the drum contents after each occasion on which the drum was opened, with consequent danger of contamination. The type of lining which is often used and might give rise to one or other of these difficulties is illustrated in fig. 1.

Fig 2—Drum with lining held in place by spring clips. The cover is shown in the lid.

These difficulties and dangers can be overcome by means of the modification illustrated in fig. 2. Six stainless-steel spring clips are spot-welded on to the drum so that the fitted lining is held out of the way of the drum user. Before sterilisation a cover (shown in the drum lid in fig. 2) is placed on top of the drum contents and the edges are tucked down between the drum contents and the lining. The first person to use the drum discards the top cover.

The modified drum illustrated has been in daily use in one operating-theatre of this hospital for two months and has been found easier to pack and unload than those with a loose lining.

A prototype drum was modified by Mr. T. E. Hotham and the modification to a standard dressing-drum was carried out by Messrs. Surgicon. The photographs are by Mr. G. R. Kerr.

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1. Medical Research Council's Working Party report, *Lancet*, 1959, i, 425.

Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

AT the Association's meeting in London on Oct. 1–3 (ending with a joint meeting with the Association of Clinical Biochemists [1]) the papers included one on changes in the hypothalamus after pituitary-stalk section or hypophysectomy, and one on antibiotics from coal.

Hypothalamus after Pituitary-stalk Section or Hypophysectomy

Dr. E. BECK and Prof. P. M. DANIEL reported 9 selected cases out of a series of 21 in which hypophysectomy or pituitary-stalk section had been undertaken for the relief of cancer in patients aged 39–70; the postoperative survival-times ranged from 3 weeks to 29 months. In all an impenetrable barrier had been placed between the hypothalamus and the pituitary fossa. The hypothalamus was cut serially and treated by various staining methods. In the short-survival cases a venous infarct containing an accumulation of amorphous neurosecretory material was seen occupying the centre of the proximal stump of the pituitary stalk. The infarct had destroyed the supraopticohypophyseal tract, the nerve-fibres of which ended in retraction bulbs above the infarct. Between 2 and 26 months after operation the stump had enlarged and become reorganised and reinnervated, large numbers of nerve-fibres being present. A prominent reticulin network throughout the stump, not normally seen, suggested that an infarct had originally been present, as did the presence of macrophages containing hæmosiderin. Many of the regenerated nerve-fibres appeared as beaded fibres in Fomori chrome-alum-hæmatoxylin preparations, thus indicating that they were carrying neurosecretory substance. This substance was also seen in the walls of blood-vessels and as Herring corpuscles of varying sizes. The structure of this reorganised and enlarged proximal stump was reminiscent of the normal posterior lobe of the pituitary gland. The pars tuberalis seemed to have hypertrophied and contained thick bundles of nerve-fibres, which were not seen in normal cases. These bundles did not contain Gomori-positive fibres. But in a considerable series of laboratory animals with pituitary-stalk section, Gomori-positive fibres were prominent in similar nerve-bundles ramifying among the glandular cells of the much-hypertrophied pars tuberalis.

The supraoptic and paraventricular nuclei which supply the bulk of the nerve-fibres to the posterior lobe of the pituitary showed some nerve-cell loss after 3 weeks, and severe cell loss accompanied by dense gliosis after longer survival—a finding contrasting with the finding of Sloper and Adams (1956) of no gliosis in their two cases with long survival. Some of the surviving nerve cells and fibres always contained Gomori-positive granules. The patient who survived for 26 months had hardly any large nerve-cells left in these nuclei. The cells of the tuberal nuclei, which give rise to the tubero-hypophyseal tract, showed a very striking appearance, being much swollen, having a curious foamy cytoplasm and excentricity of the nucleus even greater than that normally seen in neurosecretory nerve-cells.

The appearances found suggest that an attempt is being made in the proximal stump of the pituitary stalk to form a reinnervated structure resembling the posterior lobe of the pituitary gland.

Antibiotics from Coal

Prof. W. D. EVANS (Nottingham) reported that carboniferous coals have yielded antibiotic remains of the microbiological decay of plants. Collectively called 'Vitricin', they seem to exhibit prophylactic control over the incidence of coalminers' pneumoconiosis. Dusts rich in vitricin are found in mines of low incidence, and vice versa. Over 200 in-vitro tests indicated that vitricin is bacteriostatic to *Mycobacterium phlei*, *Staphylo-*

1. See *Lancet*, Oct. 10, 1959, p. 546.

coccus aureus, *Pseudomonas pyocyanea*, and the tubercle bacillus H37Rv. That vitricin might consist of phenolic bactericides was excluded at the outset. In-vivo tests in the guineapig indicated low toxicity and significant inhibition of H37Rv. The acidic content of vitricin proved toxic. The basic constituents proved inactive, but the neutral components strongly inhibited *Bacillus subtilis*, *Myco. phlei*, and *Staph. aureus*. Sixteen neutral bacteriostatic constituents of vitricin have been isolated. Serial dilution tests of vitricin against *Myco. phlei* have shown activities of up to 1 part in 19,000,000, but these are often suppressed in the presence of serum.

Vitricin also exhibits fungistatic properties and has proved active against *Aspergillus niger*, *Aspergillus terreus*, *Myrothecium verrucaria*, *Verticillium albo-atrum*, *Endoconidiophora fagacearum*, *Ceratostomella ulmi*, *Glomerella cingulata*, and *Colletotrichum trifolii*.

Investigation of the biological properties of vitricin has been limited by the small yield obtained from coal. Small samples have been processed, but these were too small for toxicity tests.

Reviews of Books

The Life and Times of Sir Charles Hastings, Founder of the British Medical Association

WILLIAM H. MCMENEMEY, D.M., F.R.C.P., D.P.M. Edinburgh: E. & S. Livingstone. 1959. Pp. 516. 50*s*.

IN 1858 the " Magna Carta of medicine in this country ", the Medical Act, received the Royal Assent. Before that date no legal distinction was drawn between a trained doctor and a quack; and it has been estimated that, until then, only one in three of the practitioners in Britain had taken the trouble to obtain a formal qualification of any kind. The orthodox profession had, however, for fifty years been trying to set its house in order. Societies for medical reform sprang up all over the country, but stage coaches were only gradually being replaced by railway trains, communications were difficult, and, lacking more than local support, most of these societies were short-lived. In support of the Bill which established the General Medical Council and a Medical Register two instruments were prominent—the British Medical Association and *The Lancet*, and two men in particular, Sir Charles Hastings and Thomas Wakley.

Dr. McMenemey has written a fine and detailed account of the negotiations, correspondence, and hard work which preceded the enactment of 1858. His researches have obviously involved hundreds of hours spent over fading minute books and contemporary newspapers, but they must have been enlivened by the polemical interchanges he describes between the two principal figures. For, though Wakley and Hastings were working for a common end, they often did not see eye to eye about the methods to be used. Wakley was preoccupied with the nepotism then rife in teaching hospitals and with the undemocratic constitution and the power of the Royal College of Surgeons and of the Society of Apothecaries—the " diploma warehouse in Lincoln's Inn " and " Rhubarb Hall " as he usually styled them. Whenever Hastings' society inclined to an alliance with either body, it came under fire no less than the other " Penny Humbug Clubs ". Nevertheless, as Dr. McMenemey reminds us in this carefully documented and attractively illustrated biography, the British Medical Association was christened, and thus designated for the first time, by Wakley, and in the pages of his " dingy hebdomadal ".

Vascular Spiders and Related Lesions of the Skin

WILLIAM BENNETT BEAN, M.D., professor of medicine, head of department of internal medicine, College of Medicine, State University of Iowa, Iowa City. Oxford: Blackwell Scientific Publications. 1959. Pp. 372. 63*s*.

THIS is a scholarly, interesting, and at times amusing personal account of the author's hobby—using that word in its best sense. Since his early clinical days Professor Bean has collected data on vascular spiders. He has discussed them with anyone who shows interest and he has combed the early descriptive literature. He has written many papers on the subject and has been largely responsible for making the importance of spider nævi and palmar erythema recognised in general medical circles. He has notes on more than 1000 persons with vascular spiders collected over a period of 20 years. Much of this book is devoted to an analysis of this lesion, but it embraces many other conditions such as hereditary hæmorrhagic telangectasia, Maffucci's syndrome, Campbell de Morgan spots, and other less closely related conditions—caput Medusæ and the Baumgarten syndrome, the auriculotemporal syndrome, and erythema ab igne. The book will appeal to dermatologists, general physicians, and those who value the unusual in medical literature.

The Clinical Evaluation of New Drugs

Editors: S. O. WAIFE, M.D., F.A.C.P., head of medical-editorial department, Lilly Research Laboratories, and associate in medicine, Indiana University School of Medicine; ALVIN P. SHAPIRO, M.D., assistant professor of clinical science and medicine, co-director, hypertension-renal clinic, University of Pittsburgh School of Medicine. New York: Hoeber-Harper. 1959. Pp. 223. $7.50.

THE pharmacological properties of a new agent can usually be fairly rapidly and accurately assessed in animals maintained under carefully controlled and standardised laboratory conditions. It is often much more difficult to determine its therapeutic value. The often uncertain natural course of the disorder being treated and the powerful influence of therapeutic suggestion are two variables that make assessment particularly difficult. Furthermore there are often ethical problems in deciding whether a clinical trial of a method of treatment is indicated, in choosing the type of patient who should be included, and in planning the necessary control observations. Difficulties of this kind can be especially disturbing if favourable claims based on inadequate evidence have already been made and a proper trial is subsequently thought desirable. Much trouble can be avoided if the initial clinical investigations are foolproof, and this book indicates how they should be carried out.

The first part describes the principles underlying the evaluation of a new remedy, and is probably the most valuable section. Emphasis is laid on the importance of the design of the trial, for if this is well planned beforehand and the experiment correctly conducted the subsequent statistical analysis is straightforward. These aspects are well described in the chapter by Lasagna and Meier. The use of inert preparations is generally essential in testing drugs supposed to afford symptomatic relief, because many patients react to placebos. Beecher thinks a group of " placebo-reactors " can consistently be distinguished and avoided in therapeutic trials, but the opposite viewpoint is advanced by Wolf. These differences of opinion, fully discussed, show how difficult evaluation of a drug can be and emphasise the necessity for rigorous control in therapeutic research.

The second part is concerned with techniques for studying the action of drugs in a selected group of disorders. A sound knowledge of the natural course of the disease being treated and an appreciation of possible sources of error in the methods employed are rightly emphasised.

British medicine has played a large part in the invention and development of clinical therapeutic trials, and at no time has it been more urgent that this work should continue. With the present rapid developments in pharmacology the scientific evaluation of new drugs should be not confined to a few academic centres but widespread throughout the country. All who have an interest in undertaking these studies will find much of value and assistance in this book.

A Synopsis of Anæsthesia (4th ed. Bristol: John Wright. 1959. Pp. 616. 27*s*. 6*d*.).—The fourth edition of Dr. J. Alfred Lee's book is warmly commended. Although the arrangement remains unchanged, the contents have been thoroughly revised and additional chapters have been interpolated on the phenothiazine derivatives and on hypothermia.

THE LANCET

LONDON 31 OCTOBER 1959

Kuru

FIVE further reports [1–5] have appeared since we referred last year [6] to early accounts of kuru, an apparently new disease which is decimating the Fore cultural and linguistic group in the Eastern Highlands of Australian New Guinea. Clinically, the disorder presents as cerebellar ataxia, and usually the patient dies after six to nine months. The tremors (*kuru* means " the shakes ") gradually increase in severity, rendering standing and walking impossible, while speech becomes unintelligible and convergent strabismus often develops. Terminally there is dysphagia and urinary and fæcal incontinence. Fortunately most of the patients become euphoric and take an interest in the efforts of their families to trace the person who is supposed to have cast a spell on them. (A victim of kuru is endowed with such social importance that hysterical mimicry is not uncommon.) SIMPSON et al.[2] believe that there is some intellectual deterioration, but this is clearly not a striking feature. Of 200 cases studied by GAJDUSEK and ZIGAS [1] almost three-quarters were in women and the remaining quarter in children, boys and girls being equally affected. Incidence declines sharply in early adolescence, and the female/male ratio increases from 7·8 : 1 at the age of 25, to 28·5 : 1 at the age of 35. The disease is rare in men and it has not been observed under the age of 4. It is apparently always fatal, though it tends to be static during pregnancy, deterioration usually following delivery. But GAJDUSEK and ZIGAS [1] have observed atypical cases in which recrudescence accompanies the onset, and remission the termination, of the menses; the patients were still alive at the time of the report. These workers have also studied 2 cases which seem to be examples of intermittent kuru.

This disease, so far as is known, affects only the Fore people and those who inter-marry with them, and it may develop in members of the tribe who have left the district. The neighbouring tribe of the Kukukuku, who are separated from the Fore people by the formidable and only recently bridged Lamari river, have never had kuru. The Wana clan, which has experienced sporadic cases for a quarter of a century, sought refuge in the country of the kuru-free Kigupa people, but the two tribes remained hostile to each other and never intermarried: kuru continued to affect the Wana tribe but not the Kigupa, and, when the former eventually left the country and continued with their usual incidence of kuru, the latter moved into the territory from which they had been displaced but no cases of kuru developed. It seems unlikely, therefore, that any environmental toxin or deficiency can be responsible. All the evidence to date favours genetic predisposition in this particular tribe. In some families several siblings have succumbed on reaching approximately the same age. ROBSON et al.[7] found that kuru developed in 75% of the adult female offspring and 25% of the child female offspring of affected women, while 25% of their male offspring eventually succumbed. The corresponding figures for the offspring of unaffected women were 50%, 7%, and 1% respectively. These findings have been ascribed to one-gene transmission as a mendelian dominant trait with incomplete penetration. Thus the disease could be expected to develop in children of either sex who were homozygous for the kuru autosomal gene; but in the heterozygous condition endocrine factors would apparently exert a modifying role, the disease appearing then only rarely in men but more commonly in women. An analysis by BENNETT et al.[5] of all the pedigrees of 5000 individuals supports the view that this disease is genetically determined.

On an earlier page of this issue Dr. WILSON and his colleagues describe a few instances of a kuru-like syndrome among the 110,000 Enga-speaking natives of the Wabag-Laiagam-Kundep region of the Western Highlands of Australian New Guinea. As in the Fore tribe, WILSON et al. also found occasional instances of Parkinson's disease, of congenital cerebellar ataxia, and of senile tremor. In addition there were other forms of tremor, some doubtless psychogenic, the whole group being designated by the people *puriripiram* or sometimes *waruwaru* (" shivers "). The work is clearly not yet sufficiently advanced to justify identifying the kuru-like variety of puriripiram with kuru; but perhaps a single mutation in Melanesians underlies both kuru and the syndrome resembling it in the Western Highlanders, even though the two peoples are 170 miles apart and are not known to be related.

FOWLER and ROBERTSON [3] have reported the neurohistological findings in 5 cases of kuru, and Klatzo et al.[4] in 12.

The main change is widespread neuronal degeneration of a somewhat unusual type. Thus, whilst NISSL's " chronic cell degeneration " is common, so also is a striking degree of cytoplasmic vacuolation. The cerebellar cortex, dentate nucleus, thalamus, and corpus striatum are principally involved, but in several instances the pontine and vestibular nuclei, the olives, and the cells of Clarke's column were affected. In both the grey and the white matter, there is fairly widespread microglial reaction, together with patchy gliosis and occasional perivascular cuffing with lymphocytes. FOWLER and ROBERTSON observed heavy damage to the dorsal spinocerebellar tracts and involvement of the cells of the anterior central gyrus. Curious plaque-like bodies were noted by KLATZO et al.

1. Gajdusek, D. C., Zigas, V. *Amer. J. Med.* 1959, **26**, 442.
2. Simpson, D. A., Lander, H., Robson, H. N. *Aust. Ann. Med.* 1959, **8**, 8.
3. Fowler, M., Robertson, E. G. *ibid.* p. 16.
4. Klatzo, I., Gajdusek, D. C., Zigas, V. *Lab. Invest.* 1959, **8**, 779.
5. Bennett, J. H., Gray, A. J., Auricht, C. O. *Med. J. Aust.* 1959, ii, 505.
6. *Lancet*, 1958, i, 92.
7. Robson, H. N., Rhodes, F. A., Bennett, J. H. Cited by D. C. Gajdusek and V. Zigas (footnote 1).

in half their cases, especially in the cerebellar cortex and less commonly in the basal ganglia and cerebral cortex (notably the insula). They seem to resemble those found in certain unusual cases,[8–11] mostly familial, in which cerebellar and extrapyramidal symptoms have been thought to be associated with dementia: such cases have been related to Alzheimer's disease. Possibly kuru should be grouped with these heredofamilial disorders. KLATZO et al. suggest that kuru resembles Creutzfeld-Jakob disease; but this disease has not been found to be familial except for one remarkable family where fourteen members were afflicted in four generations [12–14] and another where the three siblings were affected.[15]

HADLOW [16] has remarked that kuru in many ways resembles scrapie, a disease which is endemic in certain confined flocks of sheep, mostly in breeding ewes, and is transmitted to an unaffected flock by the introduction of a ram or a ewe from a flock which already has the disease.

The curious soap-bubble vacuolation of neurones, first noted in scrapie by BESNOIT and MOREL,[17] and seen to a lesser extent in other conditions (notably louping-ill [18]) and even, apparently, in normal animals,[19 20] has its counterpart in kuru; and PALMER [21] has described in scrapie extracellular roundish argyrophilic bodies which suggest a metabolic by-product similar to the plaque-like bodies noted in kuru. There are other resemblances too; but there are also differences. The principal symptom of scrapie is pruritus, suggesting perhaps a generalised disease; and it can be transmitted by injecting not only brain tissue or cerebrospinal fluid but also splenic tissue from an infected animal. Moreover our knowledge of its epidemiology, though still imperfect, does not suggest that it is only genetically determined: it may possibly be transmitted through pasture contamination [22] and it is believed that a ewe may be infected from a ram or from another ewe through a ram as intermediary.[23] Scrapie has been passaged in series through three groups of goats by intracerebral inoculation of brain or cerebrospinal fluid and has been passed back to sheep.[24] The agent passes a virus filter, withstands a temperature of 100°C for 30 minutes,[25] resists 0·35% formalin for at least 3 months,[26] and can be transmitted in series, suggesting a self-replicating agent.[27] HADLOW suggests that an attempt be made to transmit kuru to primates; and should this prove successful we would have to consider whether this disease was caused, not by chromosomal pattern, but by an agent in the nervous system which is apparently not subject to the accepted limitations of protoplasm. Such a mechanism has never hitherto been detected in man.

8. Gerstmann, J., Straussler, E., Scheinker, I. *Z. ges. Neurol. Psychiat.* 1936, **154**, 736.
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11. Corsellis, J. A. N., Brierley, J. B. *ibid.* 1954, **77**, 571.
12. Jacob. H., Pyrkosch, W., Strube, H. *Arch. Psychiat. Nervenkr.* 1950, **184**, 653.
13. Kirschbaum, W. *Z. ges. Neurol. Psychiat.* 1924, **92**, 175.
14. Meggendorfer, F. *ibid.* 1930, **128**, 337.
15. Davison, C., Rabiner, A. M. *Arch. Neurol. Psychiat.* 1940, **44**, 578.
16. Hadlow, W. J. *Lancet*, 1959, ii, 289.
17. Besnoit, C., Morel, C. *Rev. vét.* 1898, p. 397.
18. Brownlee, A. *Vet. J.* 1940, **96**, 254.
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20. Zlotuik, I., Rennie, J. C. *ibid.* 1957, **67**, 30.
21. Palmer, A. C. *Vet. Rec.* 1957, **69**, 1318.
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23. Gaiger, S. H. *in* Encyclopædia of Veterinary Medicine, Surgery and Obstetrics (edited by G. H. Wooldridge); p. 198. London, 1934.
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25. Wilson, D. R. Cited by J. T. Stamp (footnote 27).
26. Grieg, J. R. *J. comp. Path.* 1950, **60**, 263.
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Unstable Diabetes

WHILE many diabetics can be held responsible for poor control of their diabetes, having failed to follow the well-established precepts, a few run into trouble despite serious efforts by themselves and their doctor. Such patients—the so-called brittle or labile diabetics—present a challenge, especially as they are often young. Some have unrecognised renal glycosuria as well as diabetes and tend to take too much insulin in an attempt to control the glycosuria, which may be present even at normal blood-sugar levels. They then swing between hypoglycæmia and surges of hyperglycæmia. If the blood-sugar is measured at this stage there is a danger of someone further increasing the dosage of insulin and thus exaggerating the swings in blood-sugar. Sometimes this difficulty can be avoided by testing for glycosuria with less than the standard proportion of urine to water, thus decreasing the sensitivity of the test and making a positive result more indicative of a raised blood-sugar level; but at all times it is wise to avoid increasing the dose of insulin on account of apparent worsening of diabetic control in the aftermath of hypoglycæmia.

Early in the insulin era, several workers sought to relate the effect of a given number of units of insulin to the "utilisation" of a given number of grammes of carbohydrate (the so-called G/I ratio) on the assumption that this had some real meaning. Competent workers, however, obtained values varying between 1·59 to 1[1] to 22 to 1.[2 3] As early as 1924, ALLAN [2] showed in diabetic dogs that the G/I ratio rose as the amount of glucose was increased, the insulin remaining constant, and fell as the amount of insulin was increased, the glucose remaining constant. Such findings were confirmed in human diabetics given different quantities of carbohydrate and of insulin.[4 5] SOMOGYI [6] has studied this problem since about 1935. He showed that the blood-sugar and glycosuria of diabetic patients often fluctuated widely even when both the carbohydrate content of the diet and the insulin dosage were kept constant. The reasons for these fluctuations were unknown, so suitable "unmanageable" diabetics were then studied over long periods, using fractional collections of urine to show the variations in glycosuria. The mass of data so collected revealed that tides of heavy glycosuria followed periods with no glycosuria even when there were no associated symptoms of hypoglycæmia. If great care was taken to avoid the troughs of blood-sugar which preceded the peaks of hyperglycæmia and glycosuria, then the insulin requirement fell profoundly and overall control improved. In one typical case there was less glycosuria with 26 units of insulin and a high-carbohydrate diet than there had been with 90 units and a low-carbohydrate diet. Such patients were no longer "unmanageable" and were able to resume gainful employment. SOMOGYI

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2. Allan, F. N. *Amer. J. Physiol.* 1924, **67**, 275.
3. Allan, F. N. *ibid.* 1925, **71**, 472.
4. Allen, F. M. *J. metab. Res.* 1923, **3**, 61.
5. Porges, O., Adlersberg, D. Die Behandlung der Zuckerkrankheit mit fettarmer Kost. Berlin, 1929.
6. Somogyi, M. *Amer. J. Med.* 1959, **26**, 169.

concluded that the original instability had been due to excessive insulin dosage.

In one of his previously unmanageable cases he cautiously increased the dose of insulin by 6 units with the aim of eliminating the glycosuria. As a result the patient had a nocturnal hypoglycæmic attack followed by a sharp increase in glycosuria on the following day. Again he followed the conventional procedure, increasing the insulin dose by 2 units in an attempt to control the now heavy glycosuria. The blood-sugar had by then become extremely variable and some ketonuria had appeared. In view of the gross deterioration in control, initiated in this case by increasing the daily dose of insulin from 22 to 30 units, the process was reversed, with excellent effect.

The importance of avoiding even mild insulin overdosage has been confirmed at various centres,[7–10] but it seems to be only diabetics with innate instability who show such severely disturbed control after too much insulin as is described by SOMOGYI in some of his long-studied patients.

There is good evidence suggesting that the hyperglycæmic rebound following hypoglycæmia is mediated by the release of adrenaline and also of glucocorticoids,[6] which oppose the hypoglycæmic effect of insulin. So powerful is the effect of the insulin antagonists that chronic over-treatment with insulin or the presence of an insulin-secreting tumour can actually induce a diabetic type of response to a glucose-tolerance test.[11] The critical blood-sugar level at which insulin-antagonising hormones are released into the circulation seems to be about 60 to 65 mg. per 100 ml. (expressed as true glucose); so rebound hyperglycæmia can be produced without any premonitory clinical warnings of hypoglycæmia. SOMOGYI [6] therefore defines hypoglycæmia physiologically as "any blood sugar value that is measurably below the normal postabsorptive level". This, then, is the definition of hypoglycæmia which is relevant in the treatment of unstable diabetics.

Podola

PODOLA has failed in his claim that he was unfit to plead to a charge of capital murder in that he was suffering from hysterical amnesia and had lost all memory of the events with which he was charged.[12] There can be no appeal to the House of Lords because the Attorney-General has refused to give the necessary certificate under the Criminal Appeal Act, 1907. The Act provides that the Attorney-General may give his certificate if the decision of the Court of Criminal Appeal "involves a point of law of exceptional public importance". Sir REGINALD MANNINGHAM-BULLER may have been influenced by the fact that on this occasion the Court of Criminal Appeal consisted of five judges—the usual number is three—and that their decision was unanimous, but the relevance of amnesia to fitness to plead is surely one of exceptional public importance. The new Parliament is expected to abolish the curious procedure by which a convicted person's right of appeal to the highest legal tribunal depends on the fiat of a law officer of the Crown who may personally have conducted the prosecution.

In deciding whether a person suffering, as PODOLA claimed to be, from amnesia was unfit to plead, the appeal court had to consider the effect of the word "insane" as used in the Act of 1800. In this context, the word has been given a somewhat artificial meaning. It has been construed in many cases to include persons who were not insane within the McNaughten rules, but who could not follow the proceedings at their trial and could not make a proper defence, such as the deaf mute who could not read or write or follow sign language. PODOLA's case was that hysterical amnesia prevented him remembering events during the whole period material to the question whether he had committed the crime alleged.

Although the word "insane" was not strictly interpreted when it was applied to those who could not follow the trial, the appeal court considered that it would not be "in accordance with either reason or common sense to extend the meaning of the word to include persons who are mentally normal at the time of the proceedings and are perfectly capable of instructing their solicitors as to what submissions are to be put forward by their counsel". But is a person who cannot remember what happened "perfectly capable" of giving instructions to his lawyers? It ignores the possibility, mentioned by PODOLA's counsel, of accidental killing or of provocation. Criminal—and other—trials are full of surprises, and justice may not be done if the prisoner is unable through loss of memory to supply some vital information. There may be other reasons—such as those advanced by counsel for the Crown at the Old Bailey trial—for holding that amnesia does not or should not amount to unfitness to plead, but it seems unfortunate that the question should be determined by reference to the use of the word "insanity".

There will perhaps be less controversy over the rules laid down by the Court of Criminal Appeal with regard to the burden of proof where it is alleged that the prisoner is unfit to plead. In many cases, indeed, there is no dispute between the prosecution and the defence on this point. The medical profession, however, may be attracted to the suggestion made by PODOLA's counsel that the proceedings on this issue were an inquiry and not a trial and so it was wrong to introduce any principle such as the onus of proof. This idea might well be discussed further. With it is involved the question whether a jury is the most suitable tribunal to decide the issue of fitness to plead—although in this connection it must be remembered that the evidence as to PODOLA's mental condition was not entirely medical.

The Home Secretary might in due course consider appointing a committee to review the whole question of fitness to plead. It is hardly satisfactory that the courts should have to turn to a statute of 1800 on such a matter, and there is clearly scope here for Mr. BUTLER's well-known interest in reform.

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8. Lavietes, P. H., Peters, J. P. *ibid.* 1941, **2**, 170.
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11. Somogyi, M. *Amer. J. Med.* 1959, **26**, 192.
12. See *Lancet*, Oct. 3, 1959, p. 517; *ibid.* Oct. 10, p. 563; and this issue, p. 729.

Annotations

ECHO EPIDEMICS

THREE years ago we published the observations [1] of a general practitioner, Dr. W. H. Lyle, on what seemed to be a new infectious disease he had observed in his practice in Newton-le-Willows, Lancashire; and at the same time appeared a report [2] of the isolation of a new enterovirus from similar cases seen not far away in Yorkshire. These papers can now be seen as the first trickle of a stream [3] which has recorded the spread of the virus, Echo type 9, from Italy in 1956 northward across Europe. In 1957 large epidemics occurred in the Middle West of the United States,[4–6] and have since appeared in the east [7] and south of that country and also in South Africa.[8] Strangely enough the virus and the disease now seem to have almost vanished from Britain. Lyle, in a full and readable account [9] of his experience in the epidemic, describes the town and with clear charts shows the ages (ranging from childhood to 40 years) and numbers of the patients and time of onset. Almost all patients had fever and headache, but there seemed to be significant differences between the disease picture in children and in adults. Adults commonly complained of pain in the limbs and back, anorexia, and weak muscles. Children, on the other hand, were more likely to vomit or be drowsy. 42% of children and 9% of adults showed a blotchy erythematous red or purplish rash on the face and trunk; lymphadenopathy was most common in children (70%); a stiff neck was found in about a fifth of cases but Kernig's sign was less frequently present. Certain minor neurological signs, such as nystagmus, tremor, and sluggish or overbrisk tendon jerks, were noted in a small proportion of adults, but not in children. In a few patients with stiff neck the cerebrospinal fluid was examined and pleocytosis was detected. Lyle considered that 8% of adults had signs of involvement of the central nervous system and 5% of "neuritis or radiculitis". The illness was usually over in a week or so but some adults took months to recover their sound health; but there were no deaths.

A few of Lyle's patients were tested and showed evidence of infection with Echo-9 virus; and controlled clinical and epidemiological studies in Britain and the U.S.A. have shown conclusively that the virus is indeed the cause of these very varied illnesses.[4–10] Lyle's paper shows, however, how much valuable information an alert and enthusiastic general practitioner can gather, almost before the virologist has had time to catch up with events. Moreover, such a practitioner is ideally placed to recognise the full range of clinical manifestations of epidemic disease. Since a new virus causing a new syndrome has appeared in this way, it is probable that, in the course of the ebb and flow of infectious disease, the same thing will happen again. We must hope, therefore, that other watchful practitioners will recognise the new syndromes when they appear and that laboratories will seize the opportunities thus offered.

There are three points worth special emphasis in this syndrome of exanthem and meningitis or "Echo-9 disease." [11] As more cases of Echo-virus infection are studied, it seems clear that similar rashes appear in infections by other viruses of the group,[11 12] especially type 16, but also types 4 and 6. There is one recent report of rash in a child with type-18 virus in the blood [13] —a virus previously associated only with infantile diarrhœa.[14] A report [15] has also appeared of an epidemic disease with a rather different vesicular rash apparently caused by a Coxsackie A16 virus, another member of the enterovirus group. Secondly, it seems that although Echo viruses usually produce meningitis they can rarely cause more severe damage to the nervous system. Slight muscular weakness has developed occasionally in Echo-9 infections [4 9] and more often in one epidemic of Echo-6 virus infection in the U.S.A. [16]; and there are reports of isolated cases of what seemed on clinical grounds to be typical poliomyelitis in which, however, there was no laboratory evidence of infection with a poliovirus. There was instead definite evidence of infection with an Echo virus of type 2, 4, and 9, and some Coxsackie viruses.[16–20] Also, monkeys inoculated intracerebrally with Echo 6 and 16 viruses showed muscle weakness and pathological changes in the C.N.S.[21] Thirdly, it is tempting to suggest that, just as there are different degrees of neurotropism in polioviruses, so there may be different degrees and types of virulence of the Echo viruses pathogenic for man. For example, although there were thousands of cases of meningitis in the first big waves of Echo-9 infection in Italy in 1956, rashes were not seen. On the other hand, almost all Echo-9 viruses isolated during the epidemics were pathogenic for suckling mice, while the first Echo-9 viruses isolated were not associated with epidemic disease and were not pathogenic for suckling mice. Recently attempts have been made to investigate at the cellular level how these epidemic viruses differ from the earlier strains and such fundamental studies are certainly necessary if we are ever really to understand this phenomenon.

TREATMENT OF TUBERCULOSIS IN CHILDREN

TUBERCULOUS children who need admission to hospital, particularly those of school age, should be treated in groups big enough to provide adequate educational facilities. Long periods away from normal school are required, particularly now that the school population is predominantly tuberculin negative. Reorganisation is needed therefore in countries fortunate enough to have a rapidly declining incidence (a note on p. 742 describes changes which took effect this week at High Wood Hospital for Children), and this is a matter of considerable difficulty.

One suggestion [22] is that, for the treatment of children, regions might combine to form treatment centres and, in order to continue and even improve scientific

1. Lyle, W. H. *Lancet*, 1956, ii, 1042.
2. Tyrrell, D. A. J. *ibid.* p. 1028.
3. *Brit. med. J.* 1957, i, 811.
4. Sabin, A. B., Krumbiegel, E. R., Wigand, R. *Amer. J. Dis. Child.* 1958, **96,** 197.
5. Lepow, M. L., Carver, D. H. *ibid.* p. 500.
6. Prince, J. T., St. Geme, J. W., Scherer, W. F. *J. Amer. med. Ass.* 1958, **167,** 691.
7. Kibrick, S., Enders, J. F. *New Engl. J. Med.* 1958, **259,** 482.
8. Gear, J., Measroch, V. *S. Afr. med. J.* 1958, **32,** 1062.
9. Lyle, W. H. *Ann. intern. Med.* 1959, **51,** 248.
10. Tyrrell, D. A. J., Lane, R. R., Snell, B. *Quart. J. Med.* 1958, **27,** 323.
11. Sabin, A. B. *Modern Med.* 1958, **26,** 94.
12. Macrae, A. D. *Brit. med. Bull.* 1959, **15,** 210.
13. Medearis, D. N., Kramer, R. A. *J. Pediat.* 1959, **55,** 367.
14. Eichenwald, H., Ababio, A., Arky, A. M., Hartman, A. P. *J. Amer. med. Ass.* 1958, **166,** 1563.
15. Robinson, C. R., Doane, F. W., Rhodes, A. J. *Canad. med. Ass. J.* 1958, **79,** 615.
16. Kibrick, S., Meléndez, L., Enders, J. F. *Ann. N.Y. Acad. Sci.* 1957, **67,** 311.
17. Buser, M., Krech, U., Moeschlin, S. *Helv. med. acta.* 1957, **24,** 434.
18. Foley, J. F., Chin, T. P. Y., Gravelle, C. R. *New Engl. J. Med.* 1959, **260,** 924.
19. Steigman, A. J. *J. Mt Sinai Hosp.* 1958, **25,** 391.
20. Hammon, W. M., Yohn, D. S., Ludwig, E. H., Pavia, R. A., Sather, G. E., McCloskey, L. W. *J. Amer. med. Ass.* 1958, **167,** 727.
21. Arnold, J. H., Enders, J. F. *Proc. Soc. exp. Biol., N.Y.* 1959, **101,** 513.
22. Bentley, F. J. *Lancet*, 1956, ii, 83.

standards and medical teaching, these centres should be organised in conjunction with teaching hospitals. But, though the disease is further declining in this country, organisation still appears to be on a local or regional basis. Only a very small proportion of our child population is now infected, and the annual number of deaths in children under 15 in England and Wales is now under 100. In these circumstances it is not surprising that a national centre has been suggested.[23] This would provide for all the varied needs of boys and girls of all ages, whose parents would be willing to accept a degree of separation as a worthwhile price to pay for the advantages.

It seems that the desire of local and regional bodies to provide somehow or other for their own tuberculosis problem will continue to dominate the situation. Possibly the most practicable and acceptable solution would be to organise in each region, readily accessible to the main population concerned, a mixed sanatorium for men and women with a small sanatorium/school section for children. Quite often a child with tuberculosis needs treatment at the same time as, and sometimes because, a parent needs treatment too. There would be much to commend an arrangement whereby tuberculosis could in future be treated as a family disease, as indeed it always has been.

HYDATIDOSIS

THE areas with the highest known incidence of hydatidosis are southern South America, part of Oceania, the Mediterranean littoral, the eastern Mediterranean countries, and South Africa.[24] In a Hunterian lecture to the Royal College of Surgeons of England on Oct. 7, Mr. R. G. Robinson said that in New Zealand, with a population of 2 million, nearly 90 new cases of hydatidosis are admitted to hospital yearly, and the incidence has not changed in the past thirty years.[25] In Britain the incidence is far from negligible. The records of the Registrar General for England and Wales show that there were 171 deaths from hydatidosis in the years 1946–57; and Mr. Robinson estimated that in that period some 1000 new cases of the disease were admitted to hospital.

The disease is caused by the cystic stage of *Echinococcus granulosus*, the common definitive host of which is the domestic dog; hosts other than man in which the cystic stage occurs include domestic ungulates such as the ox, the pig, the sheep, and the goat. Hydatidosis is preventable by breaking the life-cycle of the parasite between the dog and the sheep. The treatment of dogs with anthelmintic drugs to expel the adult worms is not particularly satisfactory,[26] and unless treated dogs are kept free from infected offal they may be reinfected. A second method is to deny dogs access to infected offal of sheep and cattle; the proper disposal of condemned offal is therefore of paramount importance. This precaution cannot, however, prevent infection of dogs that gain access to dead sheep, which must be one of the commonest origins of infection among farm dogs. Furthermore, many farmers kill sheep for domestic consumption, and the dog receives any offal which appears abnormal. These factors may partly account for the observation that hydatid disease is commoner in Wales than elsewhere in Britain.[27]

In New Zealand a Hydatid Research Unit has been established, the first task of which has been to assess accurately the prevalence of the parasite in the animal population. There is still much to be learnt about the ways in which the eggs of this worm are transferred from dog to man; but the discovery that both rats and mice will avidly consume tapeworm eggs present in the fæces of the dog, excreting these eggs twenty-four hours later in a viable condition, may help to explain some of the hitherto obscure sources of hydatid infection in man.

Mr. Robinson has done well to draw attention to the unreasonably high toll of hydatidosis in this country. Probably the best chance of reducing the incidence is by means of publicity, persuasion, and exhortation, which should be addressed in the first place to dog-owners and perhaps the public health authorities themselves.

RELIEF OF ANGINA PECTORIS

ANGINA pectoris usually betokens ischæmic heart-disease, and careful examination will exclude the less common causes, such as anæmia, aortic-valve disease, and syphilis. Treatment unhappily remains disappointing; and, despite much research, we cannot reverse the atheroma which is the usual cause. Chevalier and Simon [1] have reviewed the management of angina, and recognise three groups of patients.

In the first are those with " chronic angina pectoris ", whose pain is constantly produced by the same circumstances of exercise or emotion; the disease is more or less static, and the aim of treatment is to rearrange the patient's life so as to avoid the precipitating factors. Obesity, if present, is treated, and, if possible, vegetable fats are substituted for animal fats, although Chevalier and Simon strongly deprecate any tendency for patients to show an interest in their serum-cholesterol level. Consequently these workers do not recommend specific measures, such as œstrogens, to lower this level. Patients in this group can commonly follow their normal occupation and enjoy such games as golf; any exercise which does not produce pain is to be encouraged. Nitrites remain the sole treatment of the anginal attack; and the patients must be taught the proper use of trinitrin, including its prophylactic employment to forestall pain during exertion. Drugs producing a persistent increase in coronary blood-flow have generally proved disappointing; but long-acting nitrites may be helpful, especially if combined with a sedative. Frequent doses are required to maintain a high blood-nitrite level, and failure to maintain a high level probably accounts for the often-poor results: the use of timed-disintegration capsules of pentaerythritol tetranitrate in twice-daily doses is reported to overcome this difficulty, and to reduce considerably the anginal attacks.[2]

By contrast the sudden development of angina, perhaps worsening over a few weeks, and often coming on at rest, strongly suggests impending infarction. Rapid deterioration in a patient whose angina has previously been at a steady level has the same significance. This state of acute coronary insufficiency requires treatment in bed with anticoagulants at least until the acute progressive phase is over.

Patients in the third group, with intractable angina, have pain at rest or on the slightest exertion; work is

23. Bentley, F. J. *Times*, Jan. 16, 1959.
24. *Tech. Rep. Ser. Wld Hlth Org.* 1959, no. 169.
25. Foster, F. H. *N.Z. med. J.* 1958, **57**, 562.
26. Taylor, E. L. *J. R. Soc. Hlth*, 1958, **78**, 664.
27. Wolfe, H. R. I. *Lancet*, 1943, i, 795.

1. Chevalier, H., Simon, J. *Amer. Heart J.* 1959, **58**, 120.
2. Kamil, M., Klinger, I. *N.Y. St. J. Med.* 1959, **59**, 3398.

usually impossible, and many of them become demoralised. Simple measures are of no avail, and for this group Chevalier and Simon advocate a step-by-step approach, with infiltration of the preaortic plexus with procaine or ligation of the internal mammary artery under local anæsthesia as the first stage. If these measures fail, myxœdema is induced with radioactive iodine; only if this is unsuccessful is one of the cardiac revascularisation operations advised—usually the Harken or Beck-1 type. Finally, if all else fails, bilateral section of the upper four posterior thoracic nerve-roots is recommended, solely to abolish pain. Whilst this is claimed to be a rational approach, it would seem more logical to determine which measure offers the best chance of success with the least risk, and to advise this in all cases; but this is easier said than done, for accurate comparison is notoriously difficult in angina pectoris, and, as we have already indicated,[3] no single procedure is at present clearly preferable to all others.

The enthusiasm following recent claims[4–6] that iproniazid greatly reduces angina has been tempered by the high incidence of side-effects and occasional jaundice. Shoshkes et al.[7] have obtained good results in a small series of patients with far smaller doses than those previously advocated. 50 mg. or less per day proved effective and was associated with considerable reduction in side-effects: liver damage was not encountered, but this is no guarantee that it cannot occur at this level.

HOW DO ANTIBIOTIC-RESISTANT STAPHYLOCOCCI ARISE?

Waisbren and Strelitzer[8] set out to discover whether administration of an antibiotic caused a change in the sensitivity of the staphylococci infecting the patient. They studied 50 patients from whom coagulase-positive staphylococci were isolated before and after treatment with one or more of all the common antibiotics. The differences between the two cultures in their sensitivity to the antibiotics were ascertained, and an attempt was made to correlate these differences with the antibiotics that were given. These workers also sought to discover whether giving more than one antibiotic at a time reduced the risk that the infecting bacteria would acquire resistance.

They recognised the difficulties inherent in their study. Without phage-typing, which they applied to only 4 pairs of cultures, they did not know whether the second isolate was of the same type as the first or could have been acquired by the patient as a new infection from the hospital environment. In each of the 4 pairs on which phage-typing was done—in all of which resistance to penicillin had increased—the second isolate was of a different type from the first. In the 14 patients from whom only staphylococci isolated from the blood were compared, there was no change in resistance. From all their sensitivity tests on the organisms from their 50 patients, Waisbren and Strelitzer had 152 instances in which bacterial sensitivity tests were made before and after antibiotics were given. In 53, the sensitivity of the staphylococci remained the same to the antibiotic that was administered; in 57, the second isolate was more resistant; and in 42 it was more sensitive. In 17 patients to whom a single antibiotic was given, 5 instances of increased resistance were found; and in 27 who received two antibiotics 14 instances of increased resistance were observed.

Without full details it is hard to assess the authors' conclusion that these figures show that combinations of antibiotics do not apparently affect the subsequent development of resistance. They consider that these results show that the administration of an antibiotic to a patient does not greatly influence the antibiotic sensitivity of infecting staphylococci. In the light of this, they explain the present dominance of antibiotic-resistant staphylococci in hospitals by invoking the organism's great capability of variation, which will continually make antibiotics obsolete. They regard this explanation as independent of the factor of antibiotic usage and a constant stimulus for the development of new anti-staphylococcal drugs.

Such development is certainly important, but it does not seem to need to be pressed in existing circumstances. On the other hand, it would be unfortunate if this interesting paper caused doctors to look away from the importance of infection of patients in hospitals with the resistant staphylococci already well established there. Moreover, the resistance pattern of the staphylococci carried by the staff of hospitals accurately indicates which antibiotics have been used in that hospital. The organisms in a patient's lesion are not the only, or perhaps the important, ones in the spread of resistant staphylococci. Sensitive staphylococci may be eliminated from the patient's nasopharynx leaving that area ready for colonisation by the resistant organisms already there or acquired from his nurse or another patient. Nor should we forget that aerosols of antibiotic may be inhaled and directly eliminate sensitive organisms from the nasopharynx.[9]

Certainly we must encourage the search for new antibiotics, but we must continually plead for the wise and restrained use of those we already have. (Barber et al.[10] reached the important conclusion that the use of two antibiotics in combination might be of value. In particular, they found that the use of novobiocin might prevent the emergence of erythromycin-resistant staphylococci.) Nor must we take a defeatist attitude in the difficult matter of eventually understanding and controlling the spread of infection in our hospitals. Accurate ascertainment of its extent is an important first step, and further progress in thought and action on that aspect is fortunately apparent.[11]

Williams et al.[12] have made a very intensive study of the relationship between nasal staphylococci and sepsis in hospital patients. Their work shows clearly the increasing colonisation of the noses of patients with resistant strains during their stay in hospital. They established, moreover, that the incidence of postoperative staphylococcal wound sepsis was 2% in 342 patients who were never nasal carriers of staphylococci, and 7·1% in 380 who were carriers at some time.

THE next session of the General Medical Council will open on Tuesday, Nov. 24, at 2.15 P.M., when Sir DAVID CAMPBELL, the president, will deliver an address. The Medical Disciplinary Committee will sit on Wednesday, Nov. 25, at 10.30 A.M.

3. *Lancet*, Oct. 24, 1959, p. 653.
4. Cesarman, T. *Arch. Inst. Cardiol. Mex.* 1957, **27**, 563.
5. Cossio, P. *Amer. Heart J.* 1958, **56**, 113.
6. Master, A. M. *ibid.* p. 570.
7. Shoshkes, M., Rothfeld, E. L., Becker, M. C., Finkelstein, A., Smith, C. C., Wachtel, F. W. *Circulation*, 1959, **20**, 17.
8. Waisbren, B. A., Strelitzer, C. L. *Amer. J. med. Sci.* 1959, **238**, 202.
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11. Coles, R. B. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 132.
12. Williams, R. E. O., Jevons, M. P., Shooter, R. A., Hunter, C. J. W., Girling, J. A., Griffiths, J. D., Taylor, G. W. *Brit. med. J.* Oct. 10, 1959, p. 658.

Special Articles

DISTRIBUTION AND DEVELOPMENT OF SMOKING HABITS *

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THE mounting volume of evidence concerning the health hazards of cigarette smoking has stimulated interest in what might loosely be called the epidemiology of smoking habits, as well as in laboratory studies of the constituents of tobacco smoke and their effects. The present paper, based on a population sampling inquiry carried out in Edinburgh, describes the distribution and development of smoking habits and some of their social correlates. In 1957 the Department of Health for Scotland issued a circular which recommended local health authorities to bring home to the public the risks of cigarette-smoking, and the health committee of the Edinburgh Corporation accordingly decided to embark on a campaign. The University Department of Public Health and Social Medicine was asked to make a preliminary survey of smoking habits.

This survey, which was made in November, 1958, had three aims: to extend knowledge about the population distribution of smoking habits; to supply those planning the health education campaign with information which might make it more effective; and to provide a baseline against which the impact of the campaign might be measured. A similar survey, based on a comparable sample of the population in May, 1959, will show how practices and attitudes shifted during the campaign.

METHOD

A sample of people whose names appeared on the Edinburgh Electoral Register were interviewed in their own homes.

A two-stage sample design was used, six of the twenty-three wards of Edinburgh being chosen systematically when the wards had been listed in order of overcrowding. 130 names were drawn from each of the six wards, to give a sample of 780. In addition 1 in 2 of the residents of these wards who would become entitled to vote only after Oct. 1, 1958, were chosen so as to provide a separate sample of people aged 21. It was thought that these young people would be able to recall particularly easily the circumstances under which they began to smoke or decided not to, and that their attitudes and beliefs concerning smoking would also be of especial interest.

The initial samples consisted of 780 adults and 222 people aged 21. Because of marriage and National Service many of the young people were no longer at the address shown in the Register, and only 125 were interviewed. 590 adults were interviewed. 11% of the adults and 27% of the young people originally chosen had died or removed. If these are excluded, on the grounds that they were no longer available for interview, the success-rate was 85% for adults and 77% for young people. The refusal-rate was 5% in the older group and 2% in the younger, but it was relatively more common for the younger people to be away from home or for the interviewer to be unable to meet them.

* Copies of the statistical tables on which this paper is based can be had from the authors at Usher Institute, Warrender Park Road, Edinburgh, 9.

PEOPLE WHO SMOKE

Sex and Age

The largest proportion of non-smokers among men was to be found among those aged 21, but above that age the proportion who had smoked regularly (i.e., at least 1 cigarette a day for as long as a year) at some time in their lives varied little. The group of men aged 55–64 included an unusually large proportion of those who had smoked regularly in the past but had since given it up. The difference may have occurred by chance; but if there was a true increase in the numbers giving up smoking at that age, it would seem that many take it up again. But although the oldest age-group contains more smokers, their average level of tobacco consumption was particularly low. This may point to a more cautious resumption of smoking among men formerly deterred on health grounds, but clearly, in an age-group very many of whose members had retired from work, considerations of cost cannot be ignored.

At all ages, a lower proportion of women than of men smoke. 74% of the adult men were current smokers and 37% of the adult women. With age the proportion of women smoking regularly increased up to the age-group 35–44, and then fell. Two factors have probably influenced this trend: a tendency for women to become regular smokers, if they do so at all, at a later age than men, and also the more recent date at which it became socially acceptable for women to smoke cigarettes. The later age at which women started smoking cannot be explained by the suggestion that there is any tendency to take up the habit after marriage; age for age there were no statistically significant differences between married and single women in the proportions who smoked regularly. Similarly, women who were in paid employment and those who were occupied only with household duties did not differ significantly in their smoking habits.

Social Class

Among the men, smoking varied between different occupational classes.

Three broad occupational categories were used—the first was the Registrar General's social classes I and II, and the clerical members of social class III; the second was the rest of social class III; the third was social classes IV and V.

A higher proportion of the men in semiskilled and unskilled manual employment were regular smokers than of those in skilled manual occupations, while the proportion was lower still among the professional and black-coated group. The proportion of men smoking 15 or more cigarettes a day was much higher in the nonskilled group than in the other two groups, in each of which it was about the same.

Among the women we found a rather different pattern. They were classified by their own occupation if single, and by their husband's occupation if married. Below the age of 55 middle-class women smoked rather less than those in the other groups, while among older women the opposite held; but the differences were not statistically significant. Probably this difference reflects attitudes prevalent round about the 1920s, when the adoption of a predominantly masculine habit of doubtful propriety was a sign of emancipation among educated women of the professional classes. In this context it may be recalled that, while lung-cancer mortality is substantially higher among men in unskilled employment than among pro-

fessional men, the positions of married women in these classes are reversed (Registrar General 1958).

Qualities and Habits

Recent studies in the U.S.A. have drawn attention (McArthur et al. 1958) to the association between non-smoking and such characteristics as industriousness, ambition, asceticism, and religious observance. In so far as these may be considered predominantly middle-class traits, a tendency towards a similar correlation may be inferred from our findings on the occupational class-distribution of smoking habits among men. Our evidence on the association between smoking habits and church attendance further confirms the American findings.

Church attendance was most closely related to non-smoking in the groups in which church-going was least common. The generalisation that people who go to church do not smoke was most nearly valid for men under 55, only a quarter of whom went to church regularly. The association was less strong in the group of older men, over half of whom were churchgoers. Among the women over 55, 67% of whom were regular churchgoers, there was no significant difference in the smoking habits of church attenders and non-attenders. Factors which distinguished smokers from non-smokers also tended to be associated with moderate as against heavy consumption of cigarettes. Thus, men who were not churchgoers were not only more likely to smoke at all, but were also more likely to smoke heavily.

We were not surprised to find that non-smoking tended to be associated with abstention from alcohol. In addition, men who took alcohol regularly—i.e., at least once a week—were much more likely to be heavy smokers. Women who did not drink at all were more likely never to have smoked and less likely to have smoked occasionally; but similar proportions in the two groups smoked regularly. The sociable atmosphere in which alcohol is usually drunk may be at least as responsible for the association between drinking and smoking as the " orality " factor (McArthur et al. 1958).

To analyse the importance of social influences, smokers were questioned about the friends with whom they had mixed when they began to smoke, and non-smokers about the friends with whom they had mixed when they were about 20 years of age. Half the non-smokers said that most of their friends at that time had smoked, but nearly 90% of those who had smoked regularly had taken up the habit among friends most of whom were smokers. The 21-year-old members of the sample were asked whether one, both, or neither of their parents smoked. In those families in which both parents were smokers, half the young people themselves smoked; but where only one or neither parent smoked, the frequency of smoking among the 21-year-olds was only just over a quarter.

STARTING TO SMOKE

The age at which the men in our sample most commonly began to smoke regularly (that is, at least 1 cigarette a day) was 16, though at this age 30% were already confirmed in the habit. The corresponding peak-age among women was 18. We found no evidence that the average age at which regular smoking begins has declined over the past twenty or thirty years. The age at which our informants began to smoke regularly varied little from one age-group to another, with the exception of women smokers of 55 or over. Four-fifths of this group did not begin to smoke regularly until they were at least 30 years of age. Our inquiry did not include anyone under 21, so it remains possible that there has been some change during the past few years.

Men in unskilled occupations were not only more likely to smoke and to smoke heavily, but also to begin to smoke at an earlier age than men in skilled employment, while those in professional or blackcoated occupations, who smoked least, were the latest starters.

17% of the smokers in semiskilled or unskilled jobs started to smoke regularly while they were still at school. Among men in non-manual employment, the corresponding proportion was only just over half as great, though men in this latter group tend to stay longer at school. Nearly a quarter of the smokers in professional and blackcoated occupations said that they first began to smoke regularly when they were in the Services; this was far less common among men in skilled manual occupations, and least common among men in unskilled jobs. Probably the most significant fact which emerged from this analysis was that over half the men started to smoke in their first job when they had newly achieved the status of wage-earners.

An attempt to discover the rate at which smoking increases once the individual has begun to smoke regularly was made by asking our informants how much they smoked during their first month of smoking and how much a year later. Only 6% of smokers consumed 10 or more cigarettes a day during their first month of regular smoking. A year later this proportion was 27%, and at the time of interview 66%. There was a wide variation in the time taken by smokers to reach their present rate of smoking.

1 smoker in 5 took between two and five years to reach their present rate of smoking. 1 in 3 took from six months to two years, just over 1 in 4 from five to twenty years, while at the extremes 10% reached their present rate in less than six months and 9% took twenty years or longer.

GIVING UP SMOKING

10% of our sample claimed that they had smoked regularly in the past but no longer did so. 2 out of every 5 gave the cost of cigarettes and 1 in 3 health as the reason which had led them to give up the habit. Only 3 people gave fear of cancer as their reason, though the overwhelming majority of the general public are aware that many doctors and scientists believe that there is a connection between cigarette-smoking and lung cancer (Cartwright and Martin 1958). About 20% of those who had given up smoking said that they had not made a deliberate decision to do so permanently, but had stopped because of illness or pregnancy, and had not resumed the habit.

Just over half of those who were still smoking regularly reported that once or more they had stopped smoking for at least a week and another 7% that they had tried to give it up but had not succeeded even for as long as a week. Of those who had ever given up smoking for a week or more, 1 in 7 claimed to have done so at least ten times.

More than two-fifths of all the smokers, when specifically asked, said that they would like to give up smoking if they could do so easily, but over half said that they would not wish to do so even then. The reasons given for wishing to stop smoking were similar to those put forward by the people who had actually stopped. Expense was mentioned by two-thirds. Only 3% mentioned fear of cancer, and over 25% gave some other health reason.

All the people who had ever given up smoking for a week or more were questioned about their most recent attempt. The usual practice was to give up smoking suddenly rather than to cut down gradually, though 12% of those who had given up smoking permanently, in that they were still not smoking at the time of interview, had done so gradually. In both groups about 1 in 4 had taken to eating sweets instead of smoking—a lower proportion perhaps than might have been expected if an "orality" factor played an important part. A fairly substantial proportion claimed to have put on weight after giving up smoking. Whereas only a third of the people who gave up smoking temporarily said they had felt better for it, nearly two-thirds of those who had not started smoking again reported a change for the better in their health. The most common improvements were in wheezing and other respiratory symptoms. Others noted an improvement in their appetite or taste for food and others thought that they had fewer coughs, colds, catarrh, and headaches, and better general health. The only adverse effects commonly attributed to stopping smoking was a feeling of irritation, boredom, or inability to relax. When questioned specifically nearly two-fifths of those who had resumed smoking and a fifth of those who had not complained about this.

While only 3% of the people who had given up smoking permanently said they had found it very difficult to do so, 1 in 5 of those who had given it up temporarily expressed this view. Those who said that they had made a deliberate decision to give up smoking but had started again were asked why. Just over a third mentioned social pressures, or said they had started again when they were at a party or on some other social occasion. A fifth gave no particular reason, merely indicating that they had changed their minds. Others said that they had made up their minds to stop smoking when they were ill and had started to smoke again when they felt better. 1 in 10 gave the strain and depression of giving up smoking as an explanation of their failure to continue; and a few who had given it up for financial reasons said that they had not saved as much as they expected, or that they had started again when they could afford it. 7% claimed to have been so upset by their increase in weight that they thought smoking preferable to obesity.

SUMMARY

A sample survey of the adult population of Edinburgh showed that 3 men in 4 and 3 women in 8 smoked regularly.

It was less common for men to have started to smoke regularly while they were still at school than when they first became wage-earners and were mixing with friends most of whom were themselves smokers. Their rate of smoking was normally low at first, but increased over a period of two to five years.

The lower the social-class level, the higher the ratio of smokers to non-smokers, the greater the proportion of heavy smokers, and the earlier the age at which regular smoking began. Further evidence of the connection between non-smoking and "middle-class respectability" was provided by the association of non-smoking with abstention from alcohol and with church attendance.

1 person in 10 claimed to have given up smoking permanently, and more than half the current smokers had made at least one attempt to do so. Smoking was more often given up on financial than on health grounds, and fear of lung cancer was rarely mentioned as a reason. Giving up smoking is usually done suddenly rather than gradually, and is commonly believed to lead to increased weight and improvement in general health, and especially relief from respiratory symptoms; less commonly, it is thought to cause irritation or depression. More than two-fifths of all smokers maintained that they would like to give up smoking if they could do so easily.

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THE MENTAL WELFARE OFFICER AND THE PSYCHIATRIST

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THE Younghusband Committee thought that, until formal courses of training for mental health officers can be arranged, they should be encouraged to take part in outpatient psychiatric clinics. Our experience of a scheme of this kind in an English agricultural county suggests that their presence at these clinics also helps to overcome some of the difficulties caused by the separation of the hospital and local-authority services.

Huntingdonshire has a population of 78,000, and its psychiatric hospital services are provided by Fulbourn Hospital and Addenbrooke's Hospital in the neighbouring county of Cambridgeshire. Fulbourn is a mental hospital and Addenbrooke's a general hospital with a pyschiatric department which is run by the two hospitals. The main outpatient clinic is at Addenbrooke's where a 24-hour service is maintained. Outpatient clinics are also held at outlying towns, including Huntingdon. This clinic is the responsibility of a psychiatrist from Fulbourn (R. A. P.), who also has under his care many of the patients admitted to the hospital from Huntingdonshire.

In January, 1957, Huntingdonshire County Council appointed two officers to the combined posts of district welfare officer (D.W.O.) and mental welfare officer (M.W.O.). As D.W.O.s, they deal largely with old people. One of them had had considerable psychiatric experience. From the outset they kept in close touch with the psychiatrist responsible for the area. They attend the weekly outpatient clinic alternate weeks, and sit with the psychiatrist while he is interviewing patients.

This may seem revolutionary and undesirable to some psychiatrists brought up on the principles of cathartic confessionals who would fear that the arrangement might prevent a full and frank history from being obtained. Despite some initial misgivings, our experience has shown that this is not so, and that any disadvantages are far outweighed by the advantages.

The M.W.O. calls the patient into the consulting-room and seats him near the psychiatrist's desk. The M.W.O. then retires to a chair in a corner behind the patient where as a rule, his

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presence is quickly forgotten. Naturally, the M.W.O. has to be discreet and tactful. He quickly learns when the flow of history-taking is inhibited by his presence, and he then makes an excuse and withdraws. Similarly, the psychiatrist can secure his withdrawal by a prearranged signal. But need for withdrawal has arisen only two or three times in two years. Again, if the patient objects to the M.W.O.'s presence he withdraws, but this has only happened once.

EARLY ADVANTAGES

In this way, the M.W.O. is in at the beginning of the case; and if, for instance, a social report is needed, he knows exactly what is wanted. He also knows the treatment prescribed and often can arrange for adequate supervision, perhaps by explaining the treatment to relatives or neighbours. His presence at the first interview paves the way for his acceptance as a friend and counsellor by patient and relatives. When home visits are necessary, he is accepted into the home instead of being kept on the doorstep explaining his presence, or being treated with fear and suspicion as the official who takes people from their family circle into a mental hospital. When outpatient electroplexy is carried out at Fulbourn Hospital, the M.W.O. arranges for transport and explains the treatment to relatives. He acts as an essential link between the psychiatrist and all the local authority services and departments, including the police. With the minimum of formality, he can find out the chances of a patient getting a house, getting a job, or being arrested.

One of the bugbears of clinical psychiatry is assessing whether a patient's belief is a delusion or not. Most psychiatrists have experienced the chagrin of accepting as a delusion something which is fact, and vice versa. The M.W.O. with his local knowledge can often help the psychiatrist here. For instance, when the seemingly ragged tramp states that he is a wealthy Fen farmer, the M.W.O. can confirm that this is indeed so, and the good rapport with the patient is preserved. The M.W.O. knows the district in which the patient lives, its culture, and its social mores. He usually knows whether there is mental illness or deficiency in the family, who is in debt, or behind with the rent, or which relative is in jail. All too often, the patient is not an accurate source of facts about himself. The presence and knowledge of the M.W.O. at the outpatient clinic increases the value of the history, and what he does not know he can quickly find out.

AFTERCARE

In remote country districts poorly served by public transport, there are many patients with whom it is difficult to keep in touch after they have been treated. The M.W.O. makes it his job to keep an eye on these people and he reports their progress, or lack of it, to the psychiatrist. When a patient leaves Fulbourn Hospital, a copy of the discharge letter to the general practitioner is sent to the medical officer of health for the district, who tells the M.W.O. of its contents, so that he can take any action recommended in it. Another of the tasks of the M.W.O. is to support the relatives when a patient is treated at home. Often these patients are old and demented, but with a suitable tranquillising drug, social help, and support, they can live happily at home. In this area where the M.W.O. is also the D.W.O., the senile patient who does not need mental-hospital treatment but cannot be looked after at home, can be dealt with under the National Assistance Act. The dual-purpose M./D.W.O. is able to appreciate all sides of these difficult problems.

The M.W.O. is accepted as a friend and confidante by many patients—even those whom he has had to remove to hospital under a legal order. When these patients return to the outpatient clinic for follow-up they often laugh with him about their disturbed behaviour. Patients soon get to know that they will get help and sympathy from him, and this is a most useful form of psychiatric first-aid. Psychiatric teaching stresses the importance of environmental manipulation in treatment, but it is rare for the psychiatrist to be in a position to do this effectively. The M.W.O., however, can carry out the psychiatrist's instructions and materially alter a patient's environment by seeing and advising relatives, employers, supervisors, and others.

The family doctors of the area appreciate the close liaison between the M.W.O., the psychiatrist, the hospital, and the outpatient clinic; and often, instead of asking for the patient to be admitted to hospital, they merely request psychiatric advice. The M.W.O. also sees that the family doctor is kept informed of his patients' progress, thus obviating the need for lengthy reports from the outpatient clinic. The doctor is also forewarned of an approaching crisis and of how to cope with it.

Whenever the M.W.O. is in doubt, he is at liberty to seek the advice of the psychiatrist, and many psychoses are aborted and crises averted by prompt action. When compulsory admission to hospital seems necessary, he can seek the psychiatrist's advice.

We have found the work rewarding and we believe that it has increased the efficiency of the service and its value to our patients.

We wish to acknowledge the sterling work of Dr. F. Houston, who was the psychiatrist primarily responsible for setting up this coordinated psychiatric service.

Dialogues of Today

I'M ALL RIGHT, HIPPOCRATES!

SOCRATES: I hear, Glauco, that some doctors say that if the State refuses to pay them as much as they think they should earn, all doctors should refuse to serve the State, and make other arrangements to treat their patients. Do you approve of that?

GLAUCO: Certainly, Socrates, for surely no one can deny a man's right to refuse to work for what he regards as an inadequate reward, and if an employer does not pay enough, he should not complain if he cannot get people to work for him. Surely to deny that is to deny an elementary principle of freedom!

SOCRATES: And does this principle apply to other workers?

GLAUCO: Certainly.

SOCRATES: And I suppose that if there is a dispute in an industry some workers will withdraw their labour because they are dissatisfied with their wages, while others, who are more easily satisfied, will prefer to remain at work?

GLAUCO: They may prefer to do so, Socrates, but if their leaders decide that all must cease to work, they *will* all cease to work, whether they want to individually or not.

SOCRATES: No doubt, then, a worker will refuse to join his trade organisation if he thinks it is likely to act against his interest?

GLAUCO: Oh, no. If a worker does not join his trade organition, he will be likely to find it impossible to get work, for his fellow-workers will refuse to work with him, and an employer, therefore, will employ only those who belong to the trade organisation.

SOCRATES: It seems to me then that no worker is free to refuse his services, as you said, for the foundation of your "principle of freedom" is that he is first compelled to join an organisation, and then to do what it orders, whether he likes it or not.

GLAUCO: The workers should be prepared to make this sacrifice, for it is only by such methods that they have been able to raise their pay and conditions to their present level.

SOCRATES: And if the workers in an industry refuse to work, does that affect only themselves, or others also?

GLAUCO: Many others, for workers in other industries which use their products will soon be unable to work also, and sometimes the life of the whole community will be disorganised.

SOCRATES: So the freedom of one set of workers to refuse to work means that many others will not be free to work, or even perhaps to travel to their work?

GLAUCO: That is the inevitable result of social organisation, and, indeed, it is a factor which the trade organisations take into account, for they hope that public inconvenience will put pressure upon the employers to give in to them.

SOCRATES: In your opinion, then, the workers who refuse to work rightly disregard the interests of other workers, and of the rest of the community?

GLAUCO: I see no alternative, Socrates, which does not interfere with the economic rights of the worker.

SOCRATES: Why, then, have not other workers, and, indeed, the whole community, the right to intervene in a particular dispute if it interferes with their own freedom to work? If we apply your principle that one set of workers is entitled to restrict the freedom of others, why should not the community restrict the freedom of the workers to organise the withdrawal of their labour? But let us apply what you have said to the doctors. Do you think that medical officers of health should withdraw their services if those who employ them refuse to increase their pay?

GLAUCO: No, for the welfare of the community would suffer if they did so.

SOCRATES: And is the same true of doctors who work in hospitals?

GLAUCO: Yes, indeed; they would not be able to withdraw.

SOCRATES: And family doctors?

GLAUCO: They would take good care that no patient suffered as a result of any alternative arrangements they might make.

SOCRATES: And what if a patient who is now paid for by the State could not afford to pay his doctor?

GLAUCO: The doctor would treat him for nothing.

SOCRATES: Is it certain that doctors would earn more if they were no longer paid by the State?

GLAUCO: By no means.

SOCRATES: I am very inexperienced in these matters, Glauco, but have we not agreed that doctors are to withdraw from the State service because they want more money?

GLAUCO: Certainly.

SOCRATES: If it is not certain that they will earn more money independently of the State, their object in withdrawing must be to compel the State to pay them more, as other workers hope by withdrawing their labour to achieve this end.

GLAUCO: Yes.

SOCRATES: And is it not true that other workers possess two weapons: their withdrawal of labour makes their employers lose money, and it causes hardship or inconvenience to the public?

GLAUCO: Yes.

SOCRATES: But since the State makes no profit out of the health service it will not lose money if the doctors withdraw from it, but rather the reverse. And you tell me that the doctors will take care to cause no hardship or inconvenience to their patients. Why, then, should their withdrawal persuade the State to pay them more?

GLAUCO: Doctors render services to the State apart from those they give their patients, so that though they will not inconvenience their patients they could easily inconvenience the State.

SOCRATES: But of what does the State consist except of patients and potential patients, and what service does a doctor render to the State which does not concern patients, and which he could withdraw without inconveniencing patients? You have been silent, so far, Eryximachus. Tell us what you think.

ERYXIMACHUS: You began, Socrates, by saying that you assumed that each worker was free to do what he thought right. I think that, whatever happens in industry, doctors would exercise that freedom if they were involved in a dispute with the State. I think, too, that many who now say they would withdraw their services would soon find that they had to choose between withdrawal and their patients' welfare, and would choose the latter. For these reasons I think withdrawal would fail.

SOCRATES: Yes, a sense of service is a serious handicap! Do you not think, Glauco, that the wisdom and prestige of your profession are likely to achieve more than methods which are already bringing even industrial workers into disrepute?

Medicine and the Law

Hysterical Amnesia not a Form of Insanity

ON Sept. 24, 1959, the defendant, one, Podola, appeared at the Central Criminal Court charged with the capital murder of a police officer.

Before he was asked to plead to the indictment his counsel told the judge that evidence was available raising the preliminary issue whether he was fit to plead to the indictment on the ground that he had completely lost his memory for all events before July 17, the day after his arrest, and that the Crown would contest that issue. The judge ruled that it was for the defence to establish that the defendant was insane so as to be unfit to plead to the indictment, and that the burden of proof would be sufficiently discharged if they could show on the balance of probabilities that he was unfit to stand his trial. Evidence was called by both sides and the jury impanelled to try the preliminary issue were asked, in the first place, to answer the specific question "Is the defendant now suffering from a genuine loss of memory covering at least all events with which he was concerned" during a certain period?

The jury answered that the defendant was not suffering from a genuine loss of memory. The judge directed them that in view of that answer and in the absence of any other evidence pointing to the defendant's insanity it was their duty to say that he was fit to stand his trial and the jury returned a verdict accordingly.

The trial on the charge of capital murder then proceeded and the defendant was convicted and sentenced to death. He did not appeal but, a petition having been submitted, the Home Secretary referred the whole case to the Court of Criminal Appeal for determination under section 19(*a*) of the Criminal Appeal Act, 1907. The defendant had relied solely on a hysterical amnesia preventing him from remembering events during the whole of the period material to the question whether he had committed the crime alleged; there was no suggestion that his mind in other respects was not a completely normal mind, his case being that that defect of memory rendered him unable properly to instruct his advisers with the consequence that he could not make "a proper defence".

The LORD CHIEF JUSTICE, reading the judgment of the full court, said that as to onus of proof, the right principles were:

(1) In all cases in which a preliminary issue as to the accused person's sanity was raised, whether contested or not, the jury should be directed to consider the whole of the evidence and be asked "Are you satisfied upon that evidence that the accused person is insane so that he cannot be tried upon the indictment?"; (2) if the contention of insanity was put forward by the defence and contested by the prosecution, there was a burden upon the defence of satisfying the jury as to his insanity, but in such a case, the onus was discharged if the jury were satisfied on the balance of probabilities that his insanity had been made out; (3) conversely, if the prosecution alleged and the defence disputed insanity, there was a burden upon the prosecution of establishing it.

As to the question whether hysterical amnesia could in law be regarded as a form of insanity within the meaning of section 2 of the Criminal Lunatics Act, 1800, the words of that section—"If any person . . . shall be insane . . . so that such person cannot be tried upon . . . indictment"—had in many cases been construed as including persons who were not insane within the McNaughten rules, but who by reason of some physical or mental defect could not follow the proceedings at the trial and so could not make a proper defence—e.g., a deaf mute unable to read or write or use or understand sign language. But they had not been applied to cover a case where the prisoner could plead to the indictment and had the physical and mental capacity to know that he had the right of challenge and to understand the case as it proceeded.

This was the first attempt in England to assert that hysterical amnesia covering the period of events, the subject of the indictment, rendered a man insane so that he could not be tried, but the Court agreed with the opinions stated and the conclusions reached by the Court of Justiciary in the Scottish case of Russell *v.* H.M. Advocate (1946 S.C.(J.) 37) in which the Lord Justice-Clerk (Lord Cooper) said "loss of memory may be an important element in leading to the conclusion that [an accused person] is insane. . . . But, if it falls short of that, loss of memory in a person otherwise normal and sane plays its full part, if it is sufficiently proved, in increasing the onus on the Crown, and in raising doubts to which it may be the duty of the jury to give effect in a verdict of acquittal after investigation of the whole case".

That did not mean that the onus on the Crown was any greater, but that a judge should point out to a jury that they must take into consideration carefully the fact that the accused could not remember the events. The practice of including within the word "insane" persons, such as a deaf mute, who from mental or physical infirmity, could not follow what was happening in a case was in accordance with reason and common sense. It was not in accordance with either reason or common sense to extend the meaning of the word to include persons who were mentally normal at the time of the hearing and were perfectly capable of instructing their solicitors as to what submission their counsel was to put forward with regard to the commission of the crime. Even if the loss of memory had been genuine, that would not of itself have rendered the defendant insane so that he could not be tried. Accordingly, the appeal was dismissed.

REGINA *v.* PODOLA. Court of Criminal Appeal: Lord Parker, *C.J.*, Hilbery, Donovan, Ashworth, and Paull, *JJ.*, Oct. 20, 1959. Counsel and solicitors: F. H. Lawton, Q.C., and R. H. S. Harvey (registrar, Court of Criminal Appeal): Maxwell Turner and J. H. Buzzard (Director of Public Prosecutions); Sir Reginal Manningham-Buller, Q.C. (Attorney-General) and J. R Cumming-Bruce (Treasury Solicitor).

J. F. LAMB
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

THE tie-less young British doctor looked a little out of place at Kensington air terminal, but more so at Prague airport where the Czech friends who met him were fully and decorously dressed. Decorum, indeed, is a hallmark not only of the Czechs but of the bus-loads of East Germans, Poles, Hungarians, Russians, and Rumanians who pour through Prague daily. The dress and manners—young people give up their seats in trams to the elderly; the absurdly stern traffic and crossing regulations, considering the small number of cars and "skútrs"; the absence of litter in the towns, though there is a good deal in the countryside where presumably Big Brother's eye is not so all-seeing; and the general lack of variety—tempt one to wonder whether it is significant that the cat, the cynic who walks by himself, is a rarity in Czechoslovakia compared to man's fawning and gregarious friend, the dog.

The care and money lavished on the splendid Baroque churches in Prague surprised us; in one hospital we visited there were apologies because the oldest block (1936) was overdue for upgrading as it had two wards with no less than 18 beds in them. Policy on separate polyclinics is changing and in future they will be built as outpatient departments at hospitals. Provision for the aged and chronic sick, admittedly insufficient, is to be made by blocks at general hospitals and not in separate chronic hospitals. Average length of stay in hospital after confinement is 6–7 days.

One blot was Cedok, the State tourist agency, whose general inefficiency confirmed my view that tourism and hotel-keeping are among the last things with which the State should meddle. At a small but excellent restaurant in Karlovy Vary (Carlsbad) some English-speaking wags had signed a commendatory note "Two Refugees from Cedok". To be fair, however, a senior man in a large Western tourist agency once told me, when in Washington and in drink, that they reckoned they were doing well if half the customers were satisfied.

"Never cross a Czech," wrote an accountant friend before we left, but this advice proved quite unnecessary, and strangers in trouble—especially, it seemed, strangers from Britain—receive many and great kindnesses from individuals. For us these more than outweighed Cedok's deficiencies and will be perhaps our most enduring memory.

* * *

This year our Society held its annual meeting in the region which is named after my Alma Mater. At one hospital which we visited the senior consultant turned out to be my old friend Huddersfield, whom I had not seen since we were residents together at the General Hospital twenty years ago. "By Jove!" he said to me, "you haven't changed a bit!" I must have shown surprise, for "Come in", he said, "I've got proof" We followed him into his office, and there on the wall was a photograph—which I had not expected ever to see again. It showed staff and students assembled in the quadrangle; there must have been 500 people all told, so that the camera has had to swing slowly from left to right to get them all in. There was the dean: there was old Freegift Nelson who was crazy about Social Credit: there was Huddersfield himself, only with more hair than he had now: and there, on the extreme left, was me, looking somewhat apprehensive. There, too, on the extreme right—beyond even Frank, the porter—was me again, this time looking jubilant. It had taken a good sprint to get round the back of the assembly.

"Frank looks pretty mad" said Huddersfield. Yes, I reflected, so well he might: to him it must have seemed just another of "them daft student tricks". Perhaps he was right, too. I have always looked back on the incident with a curious mixture of pleasure and shame.

My colleagues of the visiting Society seemed impressed, however. Each reacted in his own way. "You were a good bit thinner then", said the chap from Cambridge. "You were two-faced even in those days" was Oxford's opinion. "Early

schizoid tendencies", remarked the psychiatrist. "Do you mean to say you haven't got a copy yourself?" asked the man from Manchester. "No", I replied, "I couldn't afford one—then". "And it's out of print now", added Huddersfield The Welsh representative attempted to put a sententious end to these exchanges. "Gather ye rosebuds while ye may", said he. We were not of us quite sure what he meant to infer by this, but Huddersfield had a happy inspiration. "Come and see the rose garden", he suggested.

* * *

I should have resisted the temptation to write to the *Sunday Tidings*, even though I did have strong feelings on the subject. A colourful character who shared the same school with me, and whom I didn't like then, read my letter and turned up on my doorstep last autumn. He was jobless, penniless, about to be homeless, and would I please find somewhere for his family to live during this purely temporary reverse in his fortunes? He positively oozed big business but he was still the same immature, egocentric, and unscrupulous show-off that I had discarded in my juvenile wisdom so long ago. Within six months I had stood bail for him and he is now safely in prison for embezzlement.

Naturally I shall never write to the papers again, but even the most obscure M.O.H. is occasionally quoted in the national press, and this week the whole dreary business started again.

I have had a letter from someone whose signature I can't decipher, addressing me chumily by my second name, which no-one has ever used, hoping that Betty and I are keeping well (my wife's name is Sheila) and expressing delight at locating me after all these years. What have I been doing since we last met in Bombay in 1940? Needless to say I was not even in India in 1940.

Do I ignore the thing, reply coldly suggesting mistaken identity, or ask him straight out what *his* racket is, making clear that I no longer lend money or give guarantees to strangers or old acquaintances?

* * *

This extraordinary summer has brought autumnal crops of strawberries which have appeared in many shops. Mrs. B., who had recently had a meningoma removed from her dorsal spine, was seated in the ward preparing some of these strawberries for the patients. She was shown to the visiting senior administrative medical officer as a very excellent result, and as she sat down to continue the strawberries, he stared at them and remarked politely, "Deep freeze?" "Oh no," said the bright young staff nurse, "it was an ordinary anæsthetic, sir."

* * *

MEDICAL WARD

The windows rattled, the rain spattered the glass,
A bed creaked and the ward echoed the breathing,
Sighing, and broken murmurs of men ill, in pain.
A nurse bustled, urinal in hand.
A patient coughed and spat and slept again.
The solitary green-shaded light glowed dim.
The resident slumped wearily in his chair,
Waited, watched and listened for the end.

The patient was in coma now, and dying.
All had been tried, steroids, antibiotics, blood, the lot,
A useless drip continued to run (his chlorides had been low).
Now, his glazing eyes open, he lay twitching,
The bed shaking to his rasping, laboured breathing.
What was he thinking about? His wife? For he was married.
His work? Most surely not. Christ, perhaps? Perhaps.
Did the word gleam in his mind like the white wing
Of a seagull planing high in a thunderous sky
Above a spent swimmer?

He was gasping now, the resident hauled himself up,
Strode to the bed and, stooping above it, waited.
The end came, silence fell.
Nurses were summoned, screens were drawn, the windows
Rattled in a gust of rising wind.

Letters to the Editor

REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—A boy of 17, who had been remanded in custody on July 23, hanged himself in his cell on Aug. 19. He had been charged with a sexual offence with another boy of 13 years. Bail was refused him. Mr. Justice Elwes made the following comment at Durham Assizes: "This boy made away with himself. In a decent world an adolescent would not be prosecuted on a criminal charge arising out of a sexual offence. He would be handed over to some intelligent sympathetic person who would help him out of his difficulties. If this boy had been at a public school he would have been handled intelligently. One can only hope that reform will be made easier by this dreadful thing."

Two obstacles stand in the way of implementing the recommendations of the Wolfenden report. The first is that, according to the Home Secretary, the public has not yet expressed its opinion on the subject, and the second, that no political party regards the matter as an urgent or even as an important one.

As chairman of the Homosexual Law Reform Society I again bring this matter to the notice of the medical profession. Whilst the Church has come down courageously and strongly on the side of implementation of the Wolfenden report the medical profession, whose concern it should be, has shown very little interest in the matter. Are we, like the politicians, to go on regarding it as of very little importance? Do we wait quietly until another boy has hanged himself?

London, W.1. KENNETH WALKER.

TOXIC CHEMICALS IN AGRICULTURE

SIR,—In your issue of Oct. 10 you reported the inquest on the death of a farm-worker's wife who had drunk arsenic-contaminated water in her home. The water had become contaminated with arsenite from a potato-spraying machine during dilution of the arsenite on the farm. The jury's declaration that "these arsenical sprays should be prohibited altogether" and the resultant withdrawal of all arsenical crop sprays by one of the largest suppliers (Fisons Ltd.) probably heralds the end of the use of arsenites on potato crops.

Your columns have contained three warnings [1–3] of the widespread use and inherent dangers of arsenites as potato defoliants, and your annotation of April 4, 1959, stated "Certainly we should not defer action until someone is accidentally killed . . ."

The development, production, and marketing of agricultural chemicals is a highly organised and competitive industry, the buffer for its enthusiasm is the Ministry of Agriculture, Fisheries and Food's advisory committee on poisonous substances used in agriculture. This committee was appointed for the protection of those employed in spraying chemicals, the farmer, and the general public. Its tasks grow more formidable each year as the chemist changes his role from servant to the master of the farmer.

The failure of the Ministry of Agriculture, Fisheries and Food to prohibit the use of arsenites as defoliants merits careful consideration as to whether the general public are being adequately protected from the hazards of toxic

1. Whitehead, T. P. *Lancet*, 1957, ii, 953.
2. *ibid.* p. 1047.
3. *ibid.* 1959, i, 721.

chemicals used in agriculture. A reconsideration of the whole problem of toxic chemicals in agriculture is urgently required.

Warwick. T. P. WHITEHEAD.

CHROMOSOME STUDIES IN HUMAN LEUKÆMIA

SIR,—Many attempts have been made to separate acute and chronic leukæmia into different disease categories—e.g., to consider acute leukæmia as a variety of malignant disease but chronic leukæmia as something else. Before the findings of Dr. Baikie and his colleagues (Sept. 26) are accepted, that chromosomal abnormalities are the rule in acute leukæmia but absent in chronic leukæmia and myelomatosis, a point of interpretation should be emphasised which was not referred to in this paper. The chromosomes observed were those in cells which had come into mitosis during a brief period of in-vitro incubation of bone-marrow. In our hands [1 2] the method of in-vitro incubation gives very variable numbers of mitoses in samples of bone-marrow from cases of leukæmia. An alternative explanation of the findings of Baikie et al. may be that the cells of acute leukæmias are indeed chromosomally abnormal (as reported earlier [1] and confirmed in unpublished observations [2]) but that the cells with a normal chromosomal complement seen in the cultures of bone-marrow from cases of chronic leukæmia and myelomatosis were really normal marrow cells which must inevitably be found to some extent in aspirated bone-marrow samples. This possibility was apparently not considered, and the number of cells observed was not given, so that, unless further evidence is available, it seems to be an open question whether there are or are not chromosomal abnormalities in chronic leukæmia in man.

There has been much discussion in the past 50 years of the general significance of chromosomal abnormalities for malignant disease and much of the discussion is of little value because of its lack of precision. When considering the regular occurrence of such chromosomal abnormalities in malignant disease of reticular tissue in mice, including (pace Prof. D. W. Smithers) the animals in which the "leukæmias" first originated,[3] we discussed three possibilities: that "the cytogenetic individuality of neoplasms is of causal significance", that the "changes in chromosomal pattern were merely epiphenomena", or that the chromosome pattern is "visible evidence of consolidation by genetic change of a modification originally imposed by other means". Does the statement of Baikie et al. that the epiphenomena may arise in a grossly disordered bone-marrow imply that environmental conditions outside cells can so alter chromosomes inside cells as to produce a new race of cells with a characteristic chromosomal morphology? This is of course a heretical idea and may be none the worse for that.

The other two possibilities they mention, that the visible chromosomal changes may include the fundamental change of neoplasia or may be the consequences of a more subtle alteration in the genetic constitution of leukæmic cells, should be distinguished only with care. Grossly visible chromosomal changes do not necessarily imply gross genetic changes. Further, once the idea is accepted (Sept. 26, p. 427) that more than one genetic change must occur for a cell to become neoplastic, then it is inevitable that selective forces will lead to the predominant survival of some "stem cell" type. Genetic changes will not be limited, or progressive, according to the degree of departure from normal cell differentiation, since the degree of departure itself depends on prior genetic changes. Granted the existence of an intracellular heritable change in all cancer cells (again pace Professor Smithers), "the essential problem is how the mechanism of genetic variation was initiated" for only if there is genetic *variability* can there be a progression from fully normal to fully neoplastic cells.

M.R.C. Radiobiological Research Unit, Harwell. C. E. FORD
R. H. MOLE.

1. Ford, C. E., Jacobs, P. A., Lajtha, L. G. *Nature, Lond.* 1958, **181**, 1565.
2. Ford, C. E., Lajtha, L. G. Unpublished observations.
3. Ford, C. E., Hamerton, J. L., Mole, R. H. *J. Cell. comp. Physiol.* 1958, **52**, suppl. 1, 235.

SOMATIC CHROMOSOMES IN A CHILD WITH BONNEVIE-ULLRICH SYNDROME

SIR,—The recent demonstration by Ford and his co-workers [1] that chromatin-negative females with gonadal dysgenesis (Turner's syndrome) have 45 chromosomes with a probable sex chromosome constitution XO has prompted us to examine the somatic chromosomes of a girl of 5 years who had been recognised in early infancy to have the clinical features of the bilateral symmetrical form of Bonnevie-Ullrich syndrome. This condition is now known to be associated with gonadal dysgenesis. The clinical findings in this child during infancy have been reported previously.[2] Examination of her buccal mucosal cells has shown them to be chromatin-negative.

Iliac marrow was cultured in a way previously described,[3] and the chromosomes examined in 23 cells; of these 22 had a chromosome number of 45 and the remaining 1 a count of 44. This latter cell is thought to be one which became broken during the preparation of the slides. Detailed analysis of the chromosomes of cells of suitable quality showed them to be consistent with an interpretation of 44 autosomes and a single X chromosome, as previously reported for adult cases of Turner's syndrome.

This case demonstrates the value of the examination of chromosomes as a diagnostic test for gonadal dysgenesis before puberty.

Medical Pædiatric Department, Western General Hospital, Edinburgh. PATRICIA JACOBS
A. J. KEAY.

1. Ford, C. E., Jones, K. W., Polani, P. E., de Almeida, J. C. G., Briggs, H. J. *Lancet*, 1959, i, 711.
2. Keay, A. J., Lewis, I. C. *Arch. Dis. Childh.* 1954, **29**, 424.
3. Ford, C. E., Jacobs, P. A., Lajtha, L. G. *Nature, Lond.* 1958, **181**, 1565.

ÆTIOLOGY OF PICA

SIR,—The observation that children with perverted appetites may be suffering from iron deficiency recalls the fact that similarly perverted appetites may be found, for example, in cattle which are deficient in phosphorus. I should like to put forward the suggestion that pica, both in man and in other animals, may be a symptom of many forms of mineral deficiency, and that it has a definite biological significance. It would obviously be biologically advantageous if an animal with a mineral deficiency should seek to ingest unusual substances some of which might, on the principle of blunderbuss therapy, cure the deficiency. There is no suggestion that animals—or for that matter children—with a specific mineral deficiency will positively seek out those unusual substances most likely to cure their deficiency; iron-deficient children will not show a particular preference for eating nails, nor do phosphorus-deficient cattle show any ability to choose from among a number of white powders the one that contains phosphorus. But the ability of all normal animals to distinguish between what is edible and what is not is, when one comes to think of it, such a remarkable

phenomenon that when the ability is temporarily lost one looks for a biological explanation. This does not rule out the possibility that pica, which may have started as a result of a mineral deficiency, may subsequently become established as a bad habit, even if the deficiency is corrected.

Laboratory Animals Centre,
M.R.C. Laboratories,
Carshalton, Surrey. W. LANE-PETTER.

NEONATAL PULMONARY HYALINE MEMBRANE

SIR,—Dr. Barter (Aug. 22), I believe, has attempted to give an oversimplified explanation of hyaline membrane that is not in keeping with observations to date. Allowing for the slight difficulty in explaining how such an epithelial desquamate is moulded to the alveolar walls, Dr. Barter too lightly dismisses the presence of fibrin,[1] and I know from experiments that epithelial degeneration cannot give a Lepehne-Pickworth reaction of the intensity described and depicted in my original work; nor does it give a positive nadi reaction. Furthermore, Dr. Barter might not know of subsequent work in which I showed by spectroscopy that the membrane contains a high content of hæmoglobin.[2]

In later work[3] I postulated that the membrane is an end-result—an organised, and possibly coagulated, transudate from a "neuro-paralytically" dilated alveolar capillary bed. Nothing has yet been advanced to discount this hypothesis, and I would humbly submit that the positive identification of fibrin and hæmoglobin supports this and seems to refute the notion of an origin from epithelial debris. The finding of human remains and artefacts in Pompeii does not mean that volcanic ash and lava are composed of these.

General Hospital, Sudbury,
Ontario, Canada. MATTHEW J. LYNCH

INDUSTRIAL REHABILITATION OF SCHIZOPHRENIC PATIENTS

SIR,—The report by Dr. Wing and Mr. Giddens (Oct. 3) illustrates a big problem for the psychiatrist who first meets his patients within an institution and who must often help them later to make plans for work when they return to the community. Patients are often discharged and seek employment or return to their jobs without sufficient support from the hospital and are often overwhelmed by the stress of readjustment, and faulty habits return or symptoms recur. Or they return to their jobs only to be met by sympathetic questioning, humorous derision, or enthusiastic concern, all of which may increase their sense of differentness and hamper their satisfactory adjustment. Such problems plague not only the chronic schizophrenic but patients of all kinds, and present the psychiatrist with difficult decisions in management.

The three factors—demonstrated working ability, a realistic work setting, and the development of work habits accounting (according to the authors) for the improvement of the patients—are said to be difficult to reproduce in a mental hospital. My experiences recently as coordinater of a night ward suggest that these factors arise in other situations. Patients on this ward are those who are able to work, those nearing discharge, and others for whom work may be therapeutically valuable. During the daytime they are at their respective jobs or at school, while evenings are spent in hospital. They continue to see their doctors at conferences. In addition in group-therapy sessions they are directed or encouraged to discuss their experiences in the community at their jobs or at schools. The mutual support gained from sharing a common experience has a striking therapeutic effect and greatly helps patients not only in their work but also in their general adjustment. Such a ward also reduces the sense of isolation working patients often feel when they return to a ward in which most patients have spent their day in hospital.

This programme encourages the development of good work habits, presents the patients with realistic work situations throughout the day, and also enables the patients' ability to be demonstrated to the doctor. Patients still have the support of the hospital, their doctors, and other patients at a time when this support may be crucial.

Henry Phipps Psychiatric Clinic,
The Johns Hopkins Hospital,
Baltimore. ARI KIEV.

1. Gitlin, D., Craig, J. M. *Pediatrics*, 1956, **17**, 64.
2. Lynch, M. J. G. *J. Pediat.* 1956, **48**, 165.
3. Lynch, M. J. C., Mellor, L. D., Badgery, A. R. *ibid.* p. 602.

BEDS FOR CONFINEMENT

SIR,—May I support Mr. Roworth's plea (Oct. 10) for a coordinated maternity service, and present the salient features of 100 consecutive confinements in this practice over the past nine months or so? May I also comment on the broader implications of the words "In the present state of lack of coordination between the hospital and domiciliary (maternity) service . . ."? Firstly the facts.

Multiparous patients booked and confined at home, 54.

Primiparous patients booked and confined at home, 7.

Patients who expressly wished to be confined in hospital (either N.H.S. or private), 8.

Patients booked for home confinements and subsequently admitted *before* term, 5: 2 cases of twins, 1 pre-eclampsia (primipara, normal live birth), 1 pre-eclampsia (multipara, normal live birth), 1 acute depression.

Patients booked for hospital confinement, on obstetric, medical, or social grounds, but with continuation of domiciliary antenatal care, 13:

(*a*) *Obstetric*
(i) previous cæsarean (1).
(ii) previous postpartum hæmorrhage (3).
(iii) previous disproportion (1).
(iv) age and multiparity (1).
(v) previous transverse lie and intrauterine death (1).
(*b*) *Medical.* ? mitral stenosis (1).
(*c*) *Social.* Unmarried mothers and inadequate home conditions (5).

Patients booked for home confinement and subsequently admitted as emergencies (excluding miscarriages), 13:

(i) Acute hydramnios, obvious at 34 weeks; subsequent delivery of fœtus with multiple deformities.
(ii) Long first stage, subsequent normal delivery.
(iii) Rupture of membranes on due date, meconium-stained liquor, and muffled irregular fœtal heart-sounds; subsequent cæsarean section and live birth.
(iv) Antepartum hæmorrhage (10-15 oz.) a week before term; subsequent surgical induction and normal delivery.
(v) Scarlet fever in the home, isolated in hospital; normal delivery.
(vi) Hand presentation at 34 weeks; subsequent delivery of anencephalic fœtus.
(vii) Postmaturity (2 weeks) in primipara; admission for surgical induction.
(viii) Breech presentation in primipara at labour, thought to be vertex antenatally; subsequent breech delivery and live birth.
(ix) Transverse lie at 34 weeks, small A.P.H. at 35 weeks; subsequent antenatal care at outpatients and cæsarean section, live birth.
(x) "Quiet" ectopic at 8 weeks, excision of tube.
(xi) Carneous mole diagnosed a week before going into spontaneous labour with subsequent retention of placenta; a multipara with a distant history of postpartum hæmorrhage. Flying squad called, sent to hospital.
(xii) and (xiii) Premature labour, both at 33-34 weeks, live births, 2 lb. 8 oz. and 4 lb. 12 oz.

In all these cases admission was arranged readily, and the patients were usually discharged in 2 or 3 days (longer after cæsarean section). The premature babies were discharged after reaching about 5 lb. 8 oz.

Thus, in this small series the pattern is: (i) cases that can be safely confined at home; (ii) cases which must be booked for hospital delivery; (iii) patients who expressly wish to be confined in hospital; (iv) emergencies, with early discharge when suitable. Emergencies present no difficulty so far as admission is concerned, because normal midwifery is virtually domiciliary midwifery, and thus there is no shortage of beds.

Surely the answer is neither to confine everyone in hospital to find the abnormalities, nor to have every baby in hospital for the first four days to detect the few who will require hospital treatment, but rather to give the family doctor every possible assistance to provide efficient domiciliary care.

To give a slightly different context to Mr. Aneurin Bevan's words, " Any fool can work harder, but what we want is that people should work more intelligently ": so too any hospital department can acquire its " empire " because of a failure of a coordinated service. Perhaps I may refer to Lord Moran's speech in the House of Lords debate on the National Heatlh Service (July 2, 1958) when he said that he had no doubt that in the future the pick of the general practitioners must follow their patients into hospital and really be part of the hospital staff. What many of us demand are conditions of practice that will allow us to offer, whenever possible, the continuous care of families at home. If this is not to be, then let us face it: general practice has reached the end of the road, and the sooner acute-coryza outpatient sessions are started the better.

Swindon. D. L. REES-JONES.

X-RAY EXAMINATION OF THE SCAPHOID

SIR,—It is generally accepted that a fracture of the scaphoid (carpal navicular), without displacement, may not be demonstrable at the first X-ray examination, and when the diagnosis is doubtful the wrist is immobilised to await a further X-ray in a fortnight's time. For some time I have been of the opinion that if the first X-ray is adequate most of these fractures should be visible.

To confirm this opinion it was decided, in January, 1958, to have a scrutiny of 100 consecutive cases of suspected fracture in which the initial X-ray showed no fracture. All these cases were followed with a further X-ray after a fortnight's interval; in some cases the interval was longer. In the 100 cases there was 1 error, but subsequent examination of the original film showed that a fracture was present.

Our routine examination of the scaphoid entails four views on a 12×10 in. non-screen film, and the finished film should be examined with a magnifying glass.

X-ray Department,
Southern General Hospital,
Glasgow. R. MCG. C. CRAWFORD.

THE MYENTERIC PLEXUS IN INFANTILE HYPERTROPHIC PYLORIC STENOSIS

SIR,—We have examined thirty excised biopsy specimens of the pylorus obtained at operation for infantile hypertrophic stenosis (Rammstedt's operation), together with five normal pyloruses secured at necropsy. In addition one normal biopsy specimen was obtained from an infant subjected to other surgical procedures.

Recent work has suggested that there is a degeneration of the ganglion cells of the myenteric plexus in congenital pyloric stenosis.[1 2] We have been unable to corroborate these findings. Our biopsy material was prepared for histological examination, after fixation, by staining with the following techniques:

(1) Bielschowsky-Gros silver impregnation method; (2) Vital methylene-blue methods; (3) Osmic-acid nerve stains; (4) Luxol fast blue; (5) Einarson's gallocyanine method; (6) Cresyl violet; (7) Hæmatoxylin and eosin.

Using selective nerve stains, such as the first three methods, the ganglion cells appeared normal. No pyknotic cells were seen and the nuclei, which were normal in size and shape and placed centrally within the cell body, showed no evidence of fragmentation. Comparison with the control material revealed no obvious reduction in the number of the neurons nor an increased glial proliferation within the ganglia. The nerve-fibres within the tracts of the plexus were also normal in appearance.

Employing the cresyl violet and gallocyanine techniques used by Belding and Kernohan and by Nielsen, the microscopic appearance of the ganglion cells was suggestive of degenerative change, although in no instance was fragmentation of the nucleus observed.

Since the results obtained by the latter methods are somewhat equivocal and probably due to inadequacies in the staining techniques we believe that it is unwise to draw conclusions from such evidence alone, particularly so in regard to the ætiology of hypertrophic pyloric stenosis and its possible ætiological relationship to gastric ulceration in later life.

A detailed account of this research will be published later elsewhere.

Anatomy Department,
The University, Manchester. N. R. KIRKMAN
J. R. RINTOUL.

1. Belding, H. H., Kernohan, J. W. *Surg. Gynec. Obstet.* 1953, **97**, 322.
2. Nielsen, O. S. *Acta pædiat.* 1956, **45**, 636.

TREATMENT OF ECLAMPSIA

SIR,—It is possible to find in a modern textbook methods of treatment for eclamptic fits which are almost identical with the treatment described, for instance, in a book[1] published in 1892. Morphia and chloral were advocated then, venesection was mentioned in those days; and venesection finds a place in a recent textbook.[2] Anæsthetics (and by this I mean full-scale general anæsthesia) are mentioned by various authors either timidly and with reserve, or with actual condemnation. Obstetricians have become increasingly opposed to general anæsthesia because most eclamptic fits cease after a time anyway, many of them appear to be complicated by further anoxia to an already cyanosed patient, or actual asphyxia due to inhalation of vomit.

Maternal mortality due to eclampsia remains at an incidence which cannot be ignored, and it seems to me that mortality depends almost entirely upon the duration of anoxia. The prolonged anoxia often accepted by obstetricians as inevitable in severe or repeated fits would seldom be tolerated by an anæsthetist.

To an anæsthetist, the control of eclamptic fits offers no insuperable problem. Using thiopentone and a relaxant, the fit is brought under control at once, without necessarily abolishing spontaneous respiration. Endotracheal intubation is convenient, for it establishes a clear and controlled airway, and the depth of respiration can be assessed by observation of the rebreathing bag. The hazard of aspiration of fluid into the bronchi is diminished, for salivation is checked. Small quantities of chlorpromazine and promethiazine can then be given. Under these circumstances I have found that pethidine and powerful depressants can be avoided. This is a method which may demand the presence of the doctor at the bedside or in the labour ward for several hours, but as a junior resident obstetric officer I have been able to do this.

It seems to me that subsequent fits, in severe eclampsia where there is continued hypertension, may in fact be due to cerebral damage sustained during the initial prolonged bout of anoxia.

Forest Gate Hospital,
London, E.7. NOEL JACKSON.

NEW WORDS REQUIRED

SIR,—In the study of causes of aircraft accidents it has become important to discover all the contributory factors which seem to make human errors inevitable. Unfortunately the word " error " itself carries an emotional charge which implies condemnation, and this lack of objectivity hampers investigation, research, and, ultimately, training programmes.

The only terminology which could be free from this disadvantage would involve entirely new words and in view of the wide significance of " human error " it occurred to me that some of your readers might have invaluable ideas which could be presented at a forthcoming conference.

1. Lusk, W. T. The Science and Art of Midwifery. 1892.
2. British Obstetric and Gynæcological Practice. London, 1955.

The key new word should have the meaning of " a variation from optimum (or ideal) conduct " and should be concise with some vivid appeal on both sides of the Atlantic. Ideally it should provide a noun and an intransitive verb. In time the word should be capable of both everyday and scientific use.

My own notions have not got further than the miserable neologism " variact ". I must rely on your readers to do better.

The British Aviation Insurance Co. Ltd.,
London, E.C.3. H. CAPLAN.

PRECORDIAL CATCH (TEXIDOR'S TWINGE)

SIR,—Dr. Oski (Oct. 24) is perfectly right. The syndrome I described in my Lettsomian lecture as a pain without a name was admirably described and sensibly named four years ago by Miller and Texidor.[1]

It is strange that so few people knew this; it may be because their contribution was classed as a " clinical note " and not as an original article. They have just written another article [2] on precordial catch which a friend showed me last week, so by the time I read Dr. Oski's letter I was already in communication with Miller and Texidor. I hope it will be possible to acknowledge their contribution in reprints of *The Transactions of the Medical Society of London*, although not in the original.

I described in my lecture how I circularised fifty recently elected fellows of the Royal College of Physicians as well as several eminent cardiologists and a number of medical friends. My questionnaire specifically asked if any name for the condition was known, or any description recognised, but nobody knew about " precordial catch ", nor has anybody mentioned it in the many letters I have had from America on other matters relating to the article. Some of the people questioned said that they knew this pain as " a stitch ", but most people use the word stitch for quite a different sort of pain, so there would be confusion if that term were adopted.

I believe the description and name of this pain should be widely known, so that doctors can discuss it without being confused over names, and patients can mention it without being regarded as neurotic. Many cardiologists do not recognise the condition at all, and Dr. William Evans returned the circular I sent him with a letter saying that if he encountered anyone who described a pain like that who could give all those details about it, he would regard him as grossly neurotic and in need of psychiatric treatment.

As Miller and Texidor remark, the only importance of this pain lies in distinguishing it from other anterior chest pains of serious importance. It is remarkable how many people have the pain and how few people mention it. This may be because, though the pain is acute and arresting while it lasts, it is remarkably unharrowing and quite devoid of angor animi. It is more an interesting pain than a distressing one. Only people who have some reason to be anxious about their hearts are likely to complain.

As regards the name. Let doctors call it " precordial catch ". The name is admirable, and it does not imply any causal notions which might be refuted in a few years. It is short, descriptive, and effective. Even if other earlier descriptions are found, keep the term " precordial catch ", but so that the syndrome may be more widely known, some publicity is needed. Actors choose synonyms for this reason (stage names), and a memorable synonym, parenthetically subservient to the main title, will ensure the condition gets the recognition it needs.

Call it Texidor's Twinge, and its sale is guaranteed. The lay press will have headlines " Have You Got Texidor's Twinge? " and hundreds of sufferers will be given the illusory, but psychologically substantial, comfort of a name. I am sorry about Miller, but he has to be generous about it and make way for the man with the more arresting name.

London, W.1. RICHARD ASHER.

1. *J. Amer. med. Ass.* 1955, **159**, 1364.
2. Miller, A. J., Texidor, T. A. *Ann. intern. Med.* 1959, **51**, 461.

MILIARY TUBERCULOSIS

SIR,—Your annotation of Oct. 17 repeats by implication the inaccuracy in the paper by Emery and Lorber [1] who concluded, on the basis of an investigation into 52 cases of miliary tuberculosis, that the radiological diagnosis was unreliable. As the authors themselves inform me that their findings have been quoted in medical writings throughout the world, I would be glad if I could be allowed to put the matter in perspective.

It is true, as your annotation states, that a panel of radiologists seeing the radiographs with no further information diagnosed only 28 of the 52 proved cases. What the original article fails to declare, however, is the conditions under which these radiographs were obtained. As I was responsible for the majority of them I should point out that more than half the cases were radiographed on a self-rectified (self-suppressed) X-ray apparatus with a maximum output of 100 mA and a broad focus and therefore a long exposure time. Under these conditions it is not to be expected that resolution or definition would be so good as to show small miliary tubercles. Moreover, the investigation was a retrospective one. It is therefore false to conclude on the basis of this work that radiology is not a reliable method of diagnosing early miliary tuberculosis.

The Children's Hospital,
Sheffield. THOMAS LODGE.

THESAUROSIS FOLLOWING INHALATION OF HAIR SPRAY

SIR,—In reply to Dr. Morgan (Oct. 24) may I say that I am aware of the work of James, Scadding, and Citron and of their findings of tuberculin sensitivity in sarcoidosis? This fact, however, does not alter my position—namely, that I have never yet seen a case of sarcoidosis with such a reaction even to large doses unless it was an example of tuberculous sarcoidosis about to convert to frank pulmonary tuberculosis when positive anergy gives way to allergy. Sarcoidosis is one of the most esoteric diseases known, and in a vast connurbation like the Metropolis it is not surprising that there should be this disparity of experience.

There are about 80 possible causes of pulmonary infiltrative shadows, and it is pertinent to ask Dr. Morgan and Dr. Gupta whether they, when confronted with such a case as I have described, apply every possible test to elucidate the cause of equivocal pulmonary opacitation as an aid to diagnosis; or do they not rather use the acumen and knowledge of clinical experience to come to a reasoned judgment after they have taken all aspects of the case, and particularly the history, into consideration.

I based my opinion on an evaluation of a cogent and clear history and upon clinical and radiological findings over a period of twelve months. The time lapse of this lady's illness and recovery covered the six months during which she made vigorous use of pressure-propelled hair-sprays, and her gradual restoration to health coincided with slow resolution of the pulmonary infiltrations over the following six months. It is an axiom of clinical medicine that you do not seek an eclectic cause of illness when the obvious one is staring you in the face.

Here is an example of plain cause and effect, the affection clearing when the irritant was removed. There was not to my mind any reason to suspect the presence of beryllium sarcoidosis, histoplasmosis, or miliary tuberculosis. It is sometimes

1. Emery, J. L., Lorber, J. *Brit. med. J.* 1950, ii, 702

forgotten that patients have a right to be spared unnecessary skin tests and pleural/lung biopsies when their performance is not likely to add anything of value to the certain diagnosis. Such tests to the performer may be negligible, but to the performee they may be fraught with anxiety and alarm.

Would Dr. Morgan and Dr. Gupta have been prepared to ignore the clear history given by this intelligent patient and have gone after some diagnosis unsupported by good case-taking? I have personal knowledge of a patient who suffered for more than ten years from the effects of a piece of mutton bone impacted in a main bronchus because nobody would listen to her detailed story although she told it to those who should have known better than to disregard it. (Her condition was diagnosed as "unresolved pneumonia.") If these two gentlemen can swallow the camel of fantastic coincidence and strain at the gnat of reasonable deduction in a plain case of cause and effect strongly supported by the clinical history, they are to be warmly commended upon their powers of deglutition.

Folkestone. B. G. EDELSTON.

DETERMINATION OF 3-METHOXY-4-HYDROXYMANDELIC ACID IN URINE

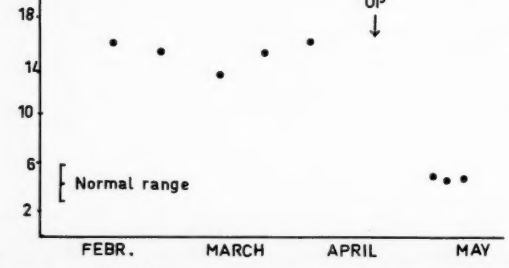
SIR,—Your leading article [1] on phæochromocytoma drew attention to 3-methoxy-4-hydroxymandelic acid (M.H.M.A.) as the major metabolite of adrenaline and noradrenaline excreted in excess in the urine of patients with phæochromocytoma. Considering its clinical importance, you regretted that no satisfactory technique for quantitative study of M.H.M.A. has yet been devised.

When Armstrong et al. identified M.H.M.A. as a major metabolite of the catechol amines we started here to elaborate a method which would allow us to measure M.H.M.A. in the urine in routine clinical work. We considered a determination of M.H.M.A. to be a much better mirror of the turnover of adrenaline and noradrenaline in the body than a catechol amine determination. Armstrong et al. used a two-dimensional paper chromatographic method, but we found this method to be fairly time-consuming and difficult to standardise for quantitative analysis.

We were able to elaborate a method by means of high-voltage electrophoresis which makes it possible in 5–6 hours to determine M.H.M.A. quantitatively. The method has been described in detail elsewhere.[2] The normal excretion of M.H.M.A. ranges between 3·2 and 5·6 mg. per 24 hours [3] (or 2·2 to 7·6 μg per mg. of creatinine [2]).

We have used this method primarily in the investigation of cases of suspected phæochromocytoma.

The accompanying figure shows M.H.M.A. excretion in a patient with this disease. After operation the excretion of M.H.M.A. went down to normal values. It is important to determine the M.H.M.A. excretion on a sample of the 24-hour output of urine, the volume of which is known. Analysis performed on individual samples voided at random may mislead the investigator as the excretion fluctuates widely. This case showed in several individual samples M.H.M.A. excretion which was only slightly higher (8·2 to 8·9 μg per mg. of creatinine) than our normal values, while the 24-hour values were 3 to 4 times greater (15–16 mg. per 24 hours) than the average normal excretion. We have also found a certain diurnal variation in the M.H.M.A. excretion with low levels during the night and morning and high values during the day and evening.[3]



Excretion of M.H.M.A. in a man of 35 with phæochromocytoma, before and after operation.

We have in addition found an excretion of M.H.M.A. above normal values (up to 15 mg. per 24 hours) in cases of myocardial infarction and burn injuries. However, this increase is only of short duration. Slight increases in the M.H.M.A. excretion have also been determined in the carcinoid syndrome,[4] paroxysmal tachycardia, and certain mental diseases. The excretion values in these cases, however, never exceeded those found in phæochromocytoma.

Department of Clinical Chemistry, General Hospital, Malmö, University of Lund, Sweden. WILFRIED VON STUDNITZ
ARNE HANSON.

TALKING SENSE

SIR,—It would be "talking sense" if it were taught that a plaster case does not necessarily cause stiffness. The belief that it does is based on a fallacy since the lesion that necessitates the plaster case provides an alternative possible cause of stiffness. If A causes B and A also causes C a statistical relationship could be discovered between B and C. But the discovery of this, however impeccable the statistics, is no proof that there is a causal relationship. In the example quoted, A, B, and C represent the lesion, the plaster case, and the stiffness respectively.

A quick method of reviewing any orthopædic paper (I can only speak for my own subject) is to assume that any sentence beginning with such phrases as "Obviously . . .", "It is well known that . . .", "There is no doubt . . .", &c., contains statements that are not obvious or are unproven, very doubtful, or positively wrong. It sometimes seems that the surest way of arriving at the truth is to search for the most strenuously held beliefs and write down their exact opposite.

Yes, I would be interested in the Section of Medical Logic mentioned by Dr. Nash (Oct. 17) although I am kept too busy trying to remedy the effects of illogic to be likely to give much time to it.

Birmingham Accident Hospital. J. H. HICKS.

"ABOUT-TURN" SYNDROME

SIR,—I recently saw a sergeant, aged 41, who was sent in as a "slipped disc". His story, however, was that while doing an energetic about-turn, his right boot caught in the ground, resulting in a sudden twist of his trunk.

Immediately after this episode he felt pain just below the right anterior superior iliac spine. During the following four days he noted increasing numbness spreading down the outside of his right thigh. He was found to have considerable diminution of all modalities of sensation in the cutaneous area exactly corresponding to that supplied by the lateral cutaneous nerve of the thigh. In addition he was tender over this nerve, as it emerged from under the lateral end of Poupart's ligament. There was no lumbar tenderness or other neurological signs.

This syndrome differs from meralgia paræsthetica, which tends to occur in rather obese middle-aged subjects and is said to be due to pressure on this nerve as it passes through the deep fascia about four inches below the

1. *Lancet*, 1959, i, 1080.
2. von Studnitz, W., Hanson, A. *Scand. J. clin. Lab. Invest.* 1959, **11**, 101.
3. von Studnitz, W. To be published.
4. von Studnitz, W. *Scand. J. clin. Lab. Invest.* (in the press).

anterior superior iliac spine. Furthermore, the sensory loss is usually less. I should be interested to know whether any of your readers have seen other examples of what I call the " about-turn " syndrome.

Tidworth Military Hospital, Hants. D. P. MULLAN.

MENTAL HEALTH SERVICES FOR GREATER LONDON

SIR,—A number of anomalies—a remnant of their historical development—have caused difficulties and have obstructed the smooth development of the mental health services in some parts of London. The greatest anomaly is the concentration of so many mental hospitals in the Epsom area and the resulting necessity for them to serve areas far away to the north and east of London. To date there has been little hope of changing this costly state of affairs short of spending many millions of pounds in building new mental hospitals. A feasible solution is that already proved experiment of day hospitals. These have proved an easy and economic way of meeting the need for psychiatric treatment in their immediate locality.

By opening 12–16 day hospitals with therapeutic hostels and workshops attached, 12,000–16,000 patients could be treated each year. This would enable the majority if not all of the patients in the whole of Greater London to be treated in the area in which they live.

In this way, without expense to the taxpayer, more convenient treatment could be provided for thousands of patients. A large proportion would receive treatment nearer their homes, so remaining in contact with their relatives. Hundreds of visitors every week would be spared incalculable travelling time and expense. The same applies to consultants and other members of the staffs who under present circumstances have to travel once or twice a week.

Unfortunately there are so many different interests involved that there is little chance for this simple plan to materialise in the foreseeable future, unless the Minister takes the bold step of forming a planning committee, who would advise him and design such an overall plan for the consideration of the regional hospital boards.

London, W.1. JOSHUA BIERER.

AN EPIDEMIC OF UNKNOWN ÆTIOLOGY

SIR,—Referring to Dr. Laidlaw's article [1] I should like to describe briefly an outbreak of an apparently " new " disease.

Within three weeks in November and December, 1958, I had 42 patients under my care in Kfar-Giladi and Kiryath-Shmone all showing a remarkably identical picture: sudden onset of severe stomach pain, heartburn, rise in body-temperature to 102·2°F (39°C) and more, accompanied sometimes by vomiting and more rarely by diarrhœa in the first hours. The pains, heartburn, and fever abated gradually in the course of four to six days. The nature and site of the abdominal symptoms were very suggestive of acute peptic ulceration, and virtually all patients gave a vivid description of hunger pains, especially at night. All patients were adults, and the sex-distribution was more or less equal. Treatment was entirely symptomatic and consisted of atropine-papaverine and aluminium hydroxide in relatively large doses. Laboratory investigations proved unhelpful, except in 2 patients in whom, on the second day, a significant hyperacidity was found: a fortnight later normal values had returned.

There is little doubt about the infectious nature of this outbreak, and because I had no better way of describing this epidemic I noted on the patients' cards " acute infectious gastritis, most probably of viral cause ".

Kfar-Giladi, Israel. DANIEL PRIDAN.

1. Laidlaw, A. J. *Lancet*, 1959, i, 1141.

PREMATURE INDUCTION AND RH-ANTIBODY TITRE

SIR,—The impression from your leader of Oct. 10 is that our paper [1] indicated that induction of labour was a risky and dangerous procedure for the mother and the fœtus. This is entirely contrary to the impression we hoped to convey, which was that our series proved that surgical induction of labour could be used in the condition indicated as a method of lowering fœtal mortality without maternal risk.

Having continued to practise the same policy regarding induction of labour, as indicated in our paper, for a further six years, we see no reason to change our opinion.

Maternity Hospital, Bellshill, Lanarkshire. R. A. TENNENT
M. D. BLACK.

*** We meant the sentence to convey no more than that premature induction was not entirely devoid of risk, and we apologise to Mr. Tennent and Mr. Black for not making this plain.—ED. L.

DIPHTHERIA TOXIN AND ANTITOXIN

SIR,—Although diphtheria has ceased to be of immediate importance in these islands and in some other parts of the world, it still has a considerable incidence in many places. From the latest figures [2] available to me, sizable numbers of cases, in some instances with a high fatality-rate, still arise in Germany, Hong Kong, Italy, Japan, Mexico, Phillipines, Poland, Portugal, South America, Turkey, Union of South Africa, United Arab Republic, and Yugoslavia.

I am tempted to recall that it is just twenty years since I sent for publication a paper [3] showing that diphtheria toxin is complex and has two antigenic components arbitrarily called at the time substance A and substance B which, together, constitute diphtheria toxin as produced by *Corynebacterium diphtheriæ* when the organism is causing infection and toxæmia in cases of diphtheria.

Substance A corresponds to the guineapig lethal factor of Park-Williams no. 8 toxin as produced in commercial, state, and international laboratories throughout the world, and used in them for all purposes related to the production and standardisation of diphtheria antitoxin and diphtheria prophylactics. In recent years, for example, by the application of Ouchterlony's [4] technique, substance A has been shown to contain a number of distinct antigenic components none of which corresponds to substance B. Substance B is produced by freshly isolated strains of *C. diphtheriæ*, especially those from severe toxic cases. It is best produced by certain gravis strains. Substance B is of low toxicity for guineapigs. These animals possess a considerable natural resistance to it, which varies with individuals. When injected intradermally into guineapigs, substance B gives an œdematous swelling which spreads slowly outwards, well beyond the limits of spread of equal injections of bland control fluids. The toxæmia found in hypertoxic cases of diphtheria is caused by a toxin composed of a relatively high proportion of substance B and relatively little guineapig lethal factor substance A. The production of substance B by freshly isolated strains of *C. diphtheriæ* was soon confirmed by Schmidt.[5]

Recently a group of American workers at Bethesda [6] have isolated, by ultracentrifugation, an antigenic component of gravis toxin which they did not find in P.W.8 toxin. This component gives œdema when inoculated intradermally in

1. Tennent, R. A., Black, M. D. *Brit. med. J.* 1954, ii, 833.
2. *Epidem. vital Statist. Rep. Wld Hlth Org.* 1958, **11**, no. 12; **12**, no. 1.
3. O'Meara, R. A. Q. *J. Path. Bact.* 1940, **51**, 317.
4. Ouchterlony, Ö. *Acta path. microbiol. scand.* 1948, **25**, 186; *Arkiv. Kemi Mineral. Geol.* 1949, **26B**, no. 14.
5. Schmidt, H. British Intelligence Objectives Subcommittee Final Report, 1946, no. 116, 73.
6. Branham, S. E., Hiatt, C. W., Cooper, A. D., Riggs, D. B. *J. Immunol.* 1959, **82**, 397.

guineapigs, identical with that described by me [3] for substance B, but apparently without spread, the œdema being confined to the limits of the weal raised by the intradermal injection. This difference may be accounted for by the very different method of preparation, or it may be that substance B, like substance A, may prove on antigenic analysis to have more than one component.

It is, however, encouraging to find that interest in the problem has begun to reach state laboratories and perhaps in these circumstances reference to the continuation of the Dublin work, beyond its initial stages, may be of value to those engaged in the preparation and standardisation of diphtheria antitoxin and prophylactics.

I had shown [3] that substance B possessed the property of rendering standard diphtheria antitoxin non-avid. Hence, in cases of hypertoxic diphtheria the antitoxin available for treatment was incapable of binding the toxin produced by the infecting organism no matter how large the dose, expressed in conventional laboratory units, administered to the patient. In these circumstances, a number of lines of approach were possible and have been summarised.[7] The two actually employed were: (*a*) to determine whether a truly avid antitoxin had, in hypertoxic cases, therapeutic properties not shown by the usual, barely avid or non-avid, commercial antitoxins; and (*b*) to determine whether avid antitoxin could be produced in animals by inoculating them with toxoids and toxins made from freshly isolated strains, in such a way as to contain a high proportion of substance B.

Both approaches gave confirmatory results. In the first it was shown by the late Dr. C. J. McSweeney,[8] using an antitoxin which I had had prepared for him to specification with a specially high avidity, as shown by its dilution ratio of 1·2, that hypertoxic diphtheria yielded to antitoxin treatment in a fashion comparable to that recorded by the pioneers of this form of treatment. The response was of an order never seen with standard commercial antitoxin. In the second [7] it was shown, by using antigens prepared from recently isolated strains of *C. diphtheriæ gravis*, that it was possible to produce both in the rabbit and the horse antitoxins which, though of low unitage as judged by the standard tests, were of quite exceptional avidity. The inevitable conclusion from these experiments is that the antibody to substance B either determines the avidity of antitoxin or else runs parallel to it.

None of these experiments is especially difficult to perform, nor are the observations difficult to make. Hence, it is apparent that the scientific approach to the problem is the direct one by transition from the clinical case, studied in all its aspects, to the infecting organism with all its infective properties preserved and thence to the laboratory, where care must be taken to see that they are not lost. By severance of laboratory investigation from the clinical case, immunology rapidly ceases to be a science in the strict sense of the term and becomes a mere technology. Doubtless the techniques which it develops are of a high order, but their benefits are commonly lost to medicine. Moreover, their unbalanced development may lead to such unnecessary absurdities as an internationally accepted unit for antitoxin of such a character that the therapeutic efficacy of antitoxin diminishes as the unitage per unit volume is raised by technical "improvements".

We have been free from significant diphtheria in these islands for many years and it is conventional to accept that the disease has been controlled by immunisation. This may be correct, but it is certain that the prophylactics used are incomplete, though possibly adequate, for protection against current strains of *C. diphtheriæ*. The disease has also disappeared for long periods in the past, before the days of prophylactics. We cannot be certain that the present satisfactory position would be maintained in the face of a renewed incursion by *C. diphtheriæ gravis* of enhanced virulence.

School of Pathology,
Trinity College,
Dublin.

R. A. Q. O'MEARA.

7. O'Meara, R. A. Q., Balch, H. H., McNally, P. A. *Irish J. med. Sci.* 6th series, 1946, p. 799.
8. McSweeney, C. J. *Lancet*, 1941, i, 208.

LEUKÆMIA IN MOTHER AND CHILD

SIR,—I was interested in your editorial of Sept. 5, at the end of which you state that no case (of leukæmia in the newborn) has been reported in which the mother had leukæmia during the pregnancy. In 1958 Cramblett, Friedman, and Najjar [1] described an infant in whom acute lymphocytic leukæmia developed at 9 months of age. The child's mother had petechiæ and ecchymoses commencing in the seventh month of pregnancy although the diagnosis of acute lymphocytic leukæmia was not established until eight days post partum.

Rochester, New York. FREDERICK HECHT.

BRILL'S DISEASE

SIR,—In your issue of Oct. 10 Dr. Lloyd and Dr. Urich discuss a case of lymphoid follicular reticulosis to which they give the eponym of Brill's disease. Many years ago Dr. Brill described an unusual form of typhus occurring in New York to which his name has been given. Who is their Brill and when was his name given as an alternative to lymphoid follicular reticulosis and by whom?

Eponyms are of interest in medicine, but surely it is absurd to use the same name twice, each for a rare disease?

Aston Clinton,
Bucks. V. E. LLOYD HART.

*** We should perhaps have encouraged our contributors to use the name Brill-Symmers disease, which *Dorland's Medical Dictionary* acknowledges as "giant follicular lympadenopathy". The Brill of both diseases was Nathan Brill, of New York, and he described,[2] with Douglas Symmers in 1925, a giant follicular hyperplasia in spleen and lymph-nodes.—ED. L.

PHARMACOLOGICAL ADJECTIVES

SIR,—The increasing flood of drugs in this era of psychopharmacology has brought into frequent use such adjectives as psychotropic, thymoplegic, thymotropic, psychotypic, psycholeptic, phrenotropic, psychotonic, ataractic, analeptic, neuroleptic, neuroplegic, thymoleptic, thymeretic, and dysleptic. As the mode of action of the new drugs is still very speculative, one wonders whether simpler terms, such as sedative, depressant, tranquilliser, stimulant, and anti-depressant, might not cover our practical needs more usefully. One fears that the multiplication of high-sounding pseudoscientific categories may weave a cloak to cover our ignorance, especially when a distinguished psychiatrist at the Cambridge Symposium last month stated that "we try to treat diseases of which we know next to nothing with drugs of which we know next to nothing". It seems that the adjectives are not even clearly understood. A recently introduced drug which many dub as "thymoleptic" is considered by other authorities to be more appropriately a "thymo-analeptic".

Park Prewett Hospital,
Basingstoke, Hampshire. I. ATKIN.

1. Cramblett, H. G., Friedman, J. L., Najjar, S. *New Engl. J. Med.* 1958, **259**, 727.
2. *J. Amer. med. Ass.* 1925, **84**, 668.

RISKS ASSOCIATED WITH MODIFIED ELECTROPLEXY

SIR,—We have been interested in this correspondence. We have used suxethonium ('Brevidil E') as a muscle relaxant in this hospital for the past three years without encountering any difficulties. The danger of fracture in electroplexy is with the first sudden tonic spasm which occurs when the electric current is passed. Our experience has taught us that a dose of 12·5 mg. of suxethonium suffices to reduce this effect on most patients, and on no occasion—even in strongly developed muscular men—would we use more than 25 mg. of this substance. We use 125 mg. of thiopentone as a routine.

Prestwich Hospital, Prestwich, Manchester.

J. P. MCGUINNESS
R. W. STARCZEWSKI.

THE CHOICE OF DIURETIC

SIR,—Your annotation of Sept. 5 states that 40 years ago Vogl discovered the first organic mercurial diuretic. May I draw your attention to the fact that the first report on the diuretic action of novasurol, the first injectable organic mercurial diuretic, was published by Saxl and Heilig [1] in 1920, and was followed by a series of investigations about the mechanism of mercurial diuresis,[2 3] whereas Vogl's story of his discovery was not published until 30 years later?

S.M.S. Medical College, Jaipur, India.

ROBERT HEILIG.

CLEAN BEDS

SIR,—In 1955 we decided to try Turkish (terry) towelling in place of woollen blankets on the beds in hospital wards because it could be boiled without shrinking. Patients found them equal in comfort to the woollen blankets. They were boiled and treated easily at the laundry, in the same way as the rest of the bed linen. The nurses found it easier to make a bed with terry towelling than with woollen blankets. A report was published [4] in 1957.

This further report shows how cotton blankets have stood up to prolonged use. When we originally tried the terry towelling, it was suggested that clean woollen blankets be supplied every month and also to each new patient. In our 1957 report we showed that we could change the towelling blankets weekly. The towelling blankets are now changed daily.

Following the success of terry towelling, I asked the Shirley Institute of the British Cotton Industry Research Association at Manchester if they could suggest any other cotton product which would be better than terry towelling. They felt that terry towelling would be extremely successful, but that we could try out a cotton cellular blanket, which we previously described under the name of a Loomstate blanket in the previous report. The correct title is really cotton cellular blanket, and I would suggest, as a standard is obviously required for comparison, that this particular blanket is referred to as the Shirley Cotton Cellular Blanket, since it was originally made and suggested by the Shirley Institute.

These were tried out in the ward, they were very easy for bedmaking and much lighter than terry towelling. The cotton cellular blankets have now been in use for $3^1/_2$ years in the plastic-surgery ward at Hemlington Hospital. They have been changed weekly so that the number of boilings at the laundry has been approximately 80 times each blanket.

3 years ago the children in the plastic ward were moved to the Stockton Children's Hospital and a ward was allocated for plastic and burns cases. This was completely equipped with terry towelling blankets, and these have been in use there for 3 years. Because of the many burns cases it was felt that a weekly change of blankets was inadequate, so they were changed daily. The result has been that the blankets in this ward have been, on an average, to the laundry 200 times. In this children's ward, the children are quite comfortable with only one terry towelling blanket on the bed. No woollen blankets have been used.

In the adults' ward where the cotton cellular and terry towelling blankets are used, one cotton cellular blanket and one terry towelling blanket give adequate warmth and comfort. The Shirley Institute has examined a typical cellular blanket after 80 boilings and a typical terry towelling blanket after 200 boilings and their findings are shown in the accompanying table. Their report says:

COMPARISON OF NEW AND USED BLANKETS

Blanket	Weight (oz./sq. yard)	Thickness (in.)	Thermal Resistance (togs)	Bulk specific volume (c.cm. per g.)
Raised wool (new) ..	14·6	0·324	2·05	16·6
Raised wool (used) ..	11·6	0·181	1·14	11·7
Cellular cotton (new) ..	9·0	0·200	1·26	16·6
Cellular cotton (used) (80 launderings) ..	10·9	0·194	1·23	13·4
Cotton terry (new) ..	15·0	0·270	1·71	13·5
Cotton terry (used) (200 launderings) ..	16·2	0·308	1·95	14·2

The tog is a unit of thermal resistance applied to clothing materials. 1 tog represents the thermal insulation provided by a textile fabric about $^1/_{16}$ in. thick.

"When new, the cellular cotton blanket is equal in ranking to the wool blanket on the warmth-to-weight basis, both being superior to the terry blanket. In single thickness, the wool blanket is thicker and therefore warmer than the cellular cotton blanket, but it is also correspondingly heavier.

"After use, both cotton blankets have shrunk, as evidenced by the increase in their weights per unit area, and whereas there has been little change in the thickness of the cellular blanket, the terry blanket has become thicker. The wool blanket, however, has lost heavily both in weight and in thickness, and there has obviously been a considerable loss of material with this blanket during laundering and use.

"We would add that the above results and comments apply to the particular blankets examined; and while they indicate the kind of changes that are likely to occur in use they should not be taken, as necessarily fully representative of the three classes of material. The construction of the blankets used may not be absolutely the best possible, but careful work should reveal any necessary technical improvement."

Bedclothes should be regarded as a part of the patient's wound dressings, and should be free from pathogenic organisms. It has been shown that by providing blankets which can be boiled and changed daily, this is possible.

It is very hard to prove that a reduction in infection in a ward is due to any one factor; but it seems correct to remove infected bedding and replace it by clean bedding as frequently as possible.

These materials have proved satisfactory, they are easy to use and laundering has caused no problems. Repairs have been few in the Turkish towelling—only 6 small repairs in 106 blankets in 3 years' use—and no repair in cotton cellular blankets.

A standard might be laid down for cotton cellular blankets in accordance with the Shirley Institute report. These materials may not prove the final answer, but careful work should lead to any necessary technical improvement.

I wish to thank the British Cotton Industry Research Association, Manchester, for their help, Dr. Leonard Colebrook for his advice, and Dr. Robert Blowers for his help with this problem.

Stockton-on-Tees.

JOHN POTTER.

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BRETYLIUM TOSYLATE

SIR,—One appreciates the difficulty of naming new products, yet the subtitle bretylium tosylate for 'Darenthin' seems unfortunate. Bretylium is not to be found in the Periodic Table nor is there a tosylic acid with which it could form a salt. In fact, scrutiny of the chemical constitution of darenthin (bromobenzyl-ethyl-dimethyl-ammonium toluene sulphonate) makes it clear how "bretylium tosylate" was arrived at. The accepted rules of chemical nomenclature seem to have been discarded in favour of pseudoscientific jargon.

Rochford General Hospital, Essex. R. G. BENIANS.

HUMIDIFICATION FOR PATIENTS WITH TRACHEOSTOMIES

SIR,—The value of tracheostomy has been increasingly recognised in the management of many conditions, including poliomyelitis,[1] tracheobronchitis,[2] and severe pulmonary disease,[3] and in connection with surgery.[4] The subject was widely discussed at the R.S.M.[5]

A common and often distressing complication of this operation is the drying and crusting of secretions in the trachea and main bronchi, due to the by-passing of the nasal and pharyngeal airways. The value of adequate humidification of the inspired air was recognised early.[1 6] Later Spalding [7] provided humidification for patients recovering respiratory activity after poliomyelitis by delivering warm humid air to the patient's tracheostomy, which was covered by a small box.

Recently at this hospital four patients with permanent tracheostomies have been treated with humidification.

Case 1 had had his laryngectomy twelve years before and had developed severe tracheitis following repair of a hernia. Case 2 was having radiotherapy to a secondary nodule in the tracheostome, his laryngectomy being eighteen months before. Cases 3 and 4 were immediately post-laryngectomy. The warm humid air stream was produced by the East blower-humidifier unit [7] and supplied to the patient via a wide-bore corrugated tube and a modified B.O.C. disposable polyethylene mask. The apparatus was usually left working continuously, the mask being removed for radiotherapy, chest radiography, &c. It was worn throughout the night by cases 1 and 2. It seemed comfortable to wear, easily adjustable by the patient, and allowed a good deal of movement; it could be worn when the patient was sitting in a chair. Cases 3 and 4 used the apparatus only intermittently during the day, usually before physiotherapy, or to assist in loosening a piece of mucus.

The disposable mask, which must be fitted with the larger (1 cm. bore) inlet tube, is modified by replacing the half-circle of soft wire in the mouth of the mask with a complete ring of similar wire. This holds the mouth of the mask open and allows of its being moulded to fit around any neck, over dressings if necessary, so as to provide a reasonably airtight fit. It is held in place with tapes or elastic, the latter simplifying access for suction.

To avoid rebreathing and consequent CO_2 retention, it is essential that an adequate volume of air be delivered to the mask. The East blower-humidifier units delivered 32–35 litres per minute but less than half this when 1 metre of 1 cm. bore tubing was added. Some 24 litres per minute were delivered if a length (1 metre) of soft (non-antistatic) corrugated rubber hose was used (for which there is a suitable outlet fitting on the humidifier). This tubing has a bigger bore, is more flexible and does not kink, and is easily supported by tapes around the patient's neck. Having a larger bore, this tubing is less liable to partial obstruction due to condensation; thus dangerously low air flows are less liable to occur.

With this rate of air flow the temperature drop between humidifier and mask was small—with the thermostat set at 48°C the temperature of the air emerging from the corrugated tube lay within 10° of that of the water in the humidifier. Mask temperatures varied between 31°C and 36°C depending on the leak of fresh air around the mask. This contrasts with the findings of Macintosh,[8] although he used a flow rate of only 8 litres per minute. In view of these findings it was felt that lagging the tubing would not really be of advantage; the tube would certainly become very cumbersome. Condensation did occur, but was not serious, provided the delivery tube was held up vertically from time to time to allow condensation to return to the humidifier, which was kept on the floor.

This apparatus is efficient, simple, and comfortable for the patient, and it avoids the discomfort of the steam tent, and the dangers of the steam kettle.

My thanks are due to Mr. C. P. Wilson and to Prof. B. W. Windeyer for allowing me to use this apparatus on their patients.

The Middlesex Hospital, London, W.1. R. BURTLES.

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Obituary

THOMAS SIDNEY NELSON

M.A., B.M. Oxon., F.R.C.P.

Dr. T. S. Nelson, who had held appointments on the staff of St. George's Hospital and the Brompton Hospital, died on Oct. 14 in London.

He was born in 1889 and educated at King's School, Canterbury, and University College, Oxford, he qualified from St. George's Hospital in 1914, and soon afterwards he joined the R.A.M.C. He served till 1918 as regimental medical officer attached to the Royal Horse Artillery, and he was mentioned in despatches. On demobilisation he returned to St. George's where he held house-posts. In 1921 he graduated B.M. and the following year obtained the M.R.C.P. After spending a year as assistant tuberculosis officer at Bristol he studied diseases of the chest, and especially tuberculosis, with a Radcliffe scholarship at the University of Pavia and at Leysin. In 1923 he was appointed assistant physician to the Brompton Hospital and two years later assistant physician to St. George's Hospital. In 1934 he was elected F.R.C.P. A year later he resigned all his hospital appointments when he became senior consulting physician to the West Middlesex Hospital. He held this post until 1942 when he resigned to work in the Emergency Medical Service at Upton Hospital, Slough. He was also appointed consulting physician to Teddington and Brentford hospitals. Apart from his hospital work he had a considerable consulting practice in diseases of the heart and lungs. In 1955 he retired and left Chiswick to live in Haslemere.

W. E. L. writes:

"During the twelve years Thomas Nelson was on the staff of the Brompton Hospital, he acquired a great reputation as a chest physician and he was particularly interested in artificial-pneumothorax therapy. It was a surprise to his colleagues to learn in 1935 that he was resigning from St. George's and the Brompton Hospitals to take up a full-time appointment at the West Middlesex Hospital. Unfortunately his plans for developing a medical unit in this large hospital were interrupted by the war, and he resigned in 1942 to continue hospital practice at a number of smaller hospitals and to return to consulting practice from his home at Chiswick. His services were much sought after. Practitioners speak warmly of him as a very able and wise consultant, and patients appreciated his kind approach to their problems.

"Tom, as his friends called him, was a man of many and varied talents. It was a pleasure to see him in his well-equipped

workshop most of which was the result of his own handiwork. He brought a keen analytical mind to bear on all he did and he set himself the highest standards. Photography was one of his early hobbies and years ago he was experimenting in colour. He was an expert craftsman in metals and wood. Sailing was a favourite pastime and he was a well-known figure at Bosham. He not only designed boats but helped to build them. When he left London for the country, he became keenly interested in his garden and the same thoroughness which had characterised his other interests soon made him an expert gardener.

"Many friends will recall the charming hospitality which he and his wife offered at their home on Chiswick Mall, especially on boat-race days."

Dr. Nelson married Dr. Mary Beaven, a fellow student at St. George's. She survives him with their daughter.

REGINALD SAMUEL SHERARD STATHAM

O.B.E., M.D., Ch.M. Brist., F.R.C.O.G.

FEW doctors can have seen so many aspects of medical practice as Dr. Reginald Statham, who died on Oct. 6 at the age of 75. In his 49 years of professional life he had served with the R.A.M.C. in two wars, held the appointment of consultant obstetrician in a teaching hospital, occupied the chair of obstetrics at Bristol, become a busy country general practitioner, and, finally, worked for many years as a member of the Pensions Appeal Tribunal.

He was the son of the Rev. S. P. H. Statham, and he was educated at Bradfield College, Berkshire. He studied medicine at Bristol and in London at the Westminster Hospital. After qualifying in 1910 he held several resident hospital appointments, including the obstetric registrarship at Bristol Royal Infirmary. In 1914 he joined the R.A.M.C. He served throughout the war and he was appointed O.B.E. for his work. After he was demobilised in 1920 he returned to his obstetrical registrarship at Bristol Royal Infirmary and two years later was appointed to the staff as assistant gynæcologist and obstetrician. In 1924 he succeeded Dr. Walter Swayne as senior gynæcologist and obstetrician, and in 1929 he became one of the foundation fellows of the Royal College of Obstetricians and Gynæcologists.

He was appointed to the chair of obstetrics in the University of Bristol in 1932, but owing to ill health he decided two years later to retire from his chair and his hospital appointments. One of his colleagues, H. J. D. S., still recalls Professor Statham's operation lists,

"as a combination of work and social entertainment, with Reggie at his best, telling rather tall stories in the anæsthetic room, ably assisted by his anæsthetist, Dr. Stuart Stock. Working closely with him while he was professor I again appreciated his happy character, fund of stories and ready welcome".

After his enforced retirement Statham faced a long illness, but he made such a remarkable recovery that he was able on his uncle's death to take over the family practice at Cheddar. During the late war he rejoined the R.A.M.C. and served from 1940 until 1946 when he was released, with the rank of colonel, on his appointment to the Pensions Appeal Tribunal.

H. L. S., writes:

"In all his activities Statham showed great interest and keenness in his work and made many friends. He had a great love for the Bristol Royal Infirmary, and under his leadership the obstetric and gynæcological department developed greatly in size and standard of work. He was a good surgeon and in teaching was one of the early enthusiasts for the use of the cinema in the instruction of medical students. He has left many pleasant memories to his patients and colleagues in Bristol and Cheddar".

Dr. Statham married in 1916 Nan Maitland Sherwin, and there was a son and a daughter of the marriage.

Notes and News

AMERICAN PUBLIC HEALTH ASSOCIATION

A THEME of this year's annual meeting of the Association, held last week at Atlantic City, was "public health is one world". Before the first general session a dinner was held jointly with the National Citizens Committee of the World Health Organisation, at which Dr. Ernest L. Stebbins, president of the committee, took the chair. At this dinner Mr. Arthur S. Flemming, Secretary of Health, Education, and Welfare, on behalf of the United States Government, handed a cheque for 3 million dollars to Dr. M. G. Candau, director-general of the World Health Organisation, and a cheque for 2 million dollars to Dr. Abraham Horwitz, director of the W.H.O. regional office for the Americas—both sums to be used for the eradication of malaria. At the second general session, with Dr. Leona Baumgartner, the president, in the chair, Mrs. Eleanor Roosevelt spoke on Peace and International Health. She commended the "Health for Peace" Bill now before the Congress, which would create a new international health research institute under the auspices of the U.S. Public Health Service, with an initial budget of 50 million dollars.

Dr. Louis T. Dublin, formerly of the Metropolitan Life Insurance Company, received the Sedgwick medal of the Association for distinguished service in public health. The Albert Lasker awards, given annually by the Albert and Mary Lasker Foundation through the Association, were made as follows:

In medical research.—Dr. Albert Coons, Dr. Gilbert Dalldorf, and Dr. Jules Freund.

In public health.—Dr. J. H. Dingle and Mr. Maurice Pate.

For extraordinary public service.—Senator Lister Hill and Congressman J. E. Fogarty.

PESTILENCES OF THE PAST

IN his presidential address to the Royal Society of Tropical Medicine and Hygiene on Oct. 15, Sir WILLIAM MACARTHUR discussed the medical identification of some pestilences of the past.

He dealt first with the plague of Athens during the second year of the Peloponnesian war. Thucydides is often noted as saying that the disease was new to the Greeks, in fact he did not do so and Sir William considered that, though its extent and fatality-rate were new, the disease could be identified as typhus, foci of which had already long existed in ancient Greece. Points enabling this identification to be carried out with a high degree of certainty were the acute onset of the fever, its association with severe delirium, and the crisis during the 11th to 20th days of its course. Further, epidemics of fever were usually more fatal to children than to adults; but to this typhus was an exception, and it is reported that, although the coma and fever affected children, the mortality among them was low. Depression, another notable feature of typhus, was common during the plague; the breath was fœtid and convulsions and ineffectual retching were also common. It was also recorded that, although the bodies of those affected were not very hot to the touch, the "internal fever was intense". The patients became delirious; some in Athens jumped into wells and in other outbreaks have been known to rise from their bed and run across fields. The identification of the disease as typhus was almost completely confirmed by the records of the ulceration and gangrene of the limbs which so commonly complicated it. Sir William compared the features of the plague of Athens with those of an outbreak of typhus in the German Army in Eastern Europe in 1943 and 1944. The maniacal delirium which developed in a third of the German patients corresponded closely with that described by Thucydides in the Athenians. Two German patients, for example, jumped from upstairs windows, and one, during a maniacal episode, thrust both hands into a coal fire. Accounts of typhus in Ireland in 1688 also revealed many points of similarity with the plague of Athens.

The pestis flava or yellow plague which affected Britain and Ireland in the middle of the 6th century had commonly been attributed to a confluent form of smallpox, but this Sir William said is incredible. The only disease which fitted the recorded description was relapsing fever.

A further pestilence to be considered was that which in the Annals of Ulster, dated 708, is called " the lameness ". This was probably poliomyelitis though the descriptions predated by 1000 years the earliest authentic references to the disease.

Sir William concluded by commenting on the accuracy of the clinical observation of physicians in ancient times. Their lack of appliances and other diagnostic tests encouraged detailed observation, and this was illustrated by old accounts of bubonic plague. If the bubo was red and increased " little by little " the prognosis was considered to be good; if it was livid or black and increased " with a swift violence " the prognosis was poor; but worst of all were those buboes " that were of a natural colour and œdematous ". These " suddenly brought the patient to destruction ".

HIGH WOOD HOSPITAL FOR CHILDREN

ON Oct. 29 High Wood Hospital for Children, Brentwood, Essex, ceased the work for which it had become justly famous among tuberculous children. On that day the last patients were transferred to Black Notley Hospital. High Wood was built in 1904 for the Metropolitan Asylums Board, originally for the treatment of children suffering from ophthalmia, and was so used until 1915, when it was loaned temporarily to the War Office. In June, 1919, the London County Council asked the Metropolitan Asylums Board to provide more accommodation for children suffering from pulmonary tuberculosis, and it was agreed to devote High Wood to this purpose, since ophthalmia was becoming less common. The hospital has since treated children suffering from pulmonary tuberculosis and, during the early years, rheumatic diseases.

In 1939 children from many London hospitals were transferred to High Wood, and a hutted annexe was built in the grounds for civilian casualties and patients bombed out of metropolitan hospitals. The huts were handed over to the London Hospital as an annexe in 1941 and are still in use. Towards the end of the war, when rockets were fired on London, the children were evacuated for a time to Stannington L.C.C. Hospital, near Morpeth, Northumberland.

Since 1919, over 10,000 tuberculous children have been treated at High Wood. In the days before chemotherapy almost half the children with the adult type of tuberculosis died within five years: in a recent similar group discharged in 1954 there was no mortality after three years and all the children were well and at work or school.[1] Much research on pulmonary tuberculosis in childhood was carried out at High Wood, a notable contribution being the publication[2] based on the after-histories of over 1000 consecutive patients. Sir Wilfrid Sheldon, in a foreword, said that High Wood was " pre-eminent in the care of tuberculous children " and that " no other centre could have supplied so much information about chronic pulmonary tuberculosis ".

Dr. C. D. S. Agassiz was medical superintendent from 1919 to 1933, when Dr. A. G. L. Reade took over, retiring in 1947. Dr. F. J. Bentley was appointed physician-superintendent in 1948, later becoming senior physician, and he will continue in charge of the High Wood Unit at Black Notley.

University of Oxford

On Oct. 15 the degree of B.M. was conferred on A. D. J. Farquharson and D. G. W. Cooper (in absentia).

University of Cambridge

On Oct. 17 the following degrees were conferred:

M.D.—* C. R. Leeson.
M.B., B.Chir.—* D. D. Devine, * D. M. C. Forster.
M.B.—* N. C. Barger, V. C. Faber, * M. T. Haslam, K. I. Mackenzie, * E. N. Wardle, * Joon Ming Yong.
* By proxy.

1. Steel, S. J., Bentley, F. J. *Tubercle* (in the press)
2. Bentley, F. J., Grzybowski, S., Benjamin, B. Tuberculosis in Childhood and Adolescence. N.A.P.T., London, 1954.

University of London

The title of professor of virology has been conferred on Dr. Forrest Fulton in respect of his post at the London School of Hygiene and Tropical Medicine.

Dr. Fulton graduated B.M. Oxon. in 1939 and soon afterwards joined the scientific staff of the Medical Research Council. During the war he worked with A. M. Begg on the relationship of the murine and epidemic types of rickettsiæ, and their relationship with proteus OX 19. He was a member of a team which investigated different laboratory methods of estimating the potency of typhus vaccines, and he was part-author of the report to the Medical Research Council in 1946 on *Chemotherapeutic and other Studies of Typhus.* Previously he had worked on diphtheria immunisation, staphylococcal toxins, and neonatal diarrhœa. Dr. Fulton took his D.M. in in 1945. He was appointed reader at the London School of Hygiene and Tropical Medicine four years later.

The title of professor of epidemiology in the University of London has been conferred on Dr. D. D. Reid in respect of his post at the London School of Hygiene and Tropical Medicine.

Dr. Reid qualified from the University of Aberdeen in 1937. After holding house-appointments at the Northern Infirmary, Inverness, he joined the research staff of the directorate general of R.A.F. Medical Services and was a member of a team studying psychological disorders in flying personnel. After the war, with a Rockefeller travelling fellowship, he worked at the University of California, where he held a visiting associate professorship in biostatistics. Soon after his return he was appointed reader at the London School of Hygiene and Tropical Medicine. He took his M.D. Aberd. with commendation in 1946 and his PH.D. Lond. three years later. He is chairman of the epidemiological panel of the National Coal Board. In 1957 he gave the Milroy lectures to the Royal College of Physicians of London, on environmental factors in respiratory disease; and his other published work includes papers on statistical and epidemiological methods in occupational medicine.

Dr. J. A. Black has been appointed senior lecturer in child health, and Dr. James Lister senior lecturer in pædiatric surgery, at the Institute of Child Health.

University of Leeds

Dr. E. P. Fitton has been appointed lecturer in the departments of anæsthetics. The title of emeritus professor has been conferred on Prof. T. Talmage Read, L.R.C.P.E., on his retirement from the chair of clinical dental surgery and wardenship of the dental school and hospital.

Royal College of Surgeons of England

On Thursday, Nov. 12, at the college, Lincoln's Inn Fields, London, W.C.2, at 5 P.M., Mr. A. Dickson Wright will give a Bradshaw lecture. He will speak on surgery of the biliary passages.

Royal College of Surgeons of Edinburgh

At the annual meeting of the college, held on Oct. 21, the following office-bearers were elected :

President, Prof. John Bruce; vice-presidents, Prof. Norman Dott, and Mr. Walter Galbraith; secretary, Mr. C. W. A. Falconer; treasurer, Mr. J. J. Mason Brown; president's council, Mr. R. S. Barclay, Mr. J. R. Cameron, Dr. J. B. Dewar, Prof. D. M. Douglas, Mr. E. L. Farquharson, Mr. J. N. J. Hartley, Prof. R. J. Kellar, Dr. R. G. Macbeth, Dr. D. S. Middleton, Mr. J. A. Ross, Prof. G. I. Scott, Mr. J. A. Shepherd, Mr. T. I. Wilson; representative on the General Medical Council, Mr. K. Paterson Brown; conservator of museum, Prof. E. C. Mekie; hon. librarian, Sir Walter Mercer.

The following were admitted to the fellowship:

I. R. Beavis, Girish Trikambhai Bhagat, W. P. Black, I. S. Brown, J. McK. Buchanan, Kong Thoe Chan, I. J. Cunningham, Jeevan Lal Hari Charan Das, A. G. Senarath Dassenaike, Sath Paul Dhanda Pravinkumar Dinkerrai Doshi, D. S. Eastwood, J. Khodadad Fozdar, Ramniklal Kirchand Gandhi, J. M. Gate, I. E. Gillespie, Craig Grant, Jogindra Lal Gupta, J. J. Handler, F. J. Harvey, K. T. Hesketh, J. F. Hickey, Kamal Vyankatrao Honavar, C. H. A. Hoy, F. E. S. Keiller, G. A. Lawrence, I. N. Lee, D. S. Leitch, J. A. London, J. M. Main, H. H. Massie, Pradip Mazumder, Panikos E. Michaelides, C. J. E. Monk, Maung Pe Nyun, A. G. Perina, D. J. D. Perrins, Mathew Philip, Sivathanu Subramania Pillai, T. S. Russell, J. Sr. George, Mutyam Venkateswara Sarma, P. R. Scott, Mehyie El Din Sedky, Mohinder Nath Sharma, Veredrra Nath Sharma, Rameshchandra Kalidas Shelat, F. F. Silk, Kuldip Singh, C. L. Smith, Mahan Vir Sood, T. G. Sprunt, N. G. Sutherland, P. W. Tapsell, J. R. Thomson, R. M. Tooth, H. C. van der Post, E. J. van Heerden, P. Chitambaranathan Vanniasingham, Hari Narain Verma, H. J. K. Vieyra, F. R. Wilson, Soon Kai Wong.

University of Birmingham

Dr. Gordon Cumming and Dr. L. A. G. Davidson have been appointed lecturers in medicine.

Royal Faculty of Physicians and Surgeons of Glasgow

On Sept. 29, Sir Maurice Bloch opened the lecture theatre which is to bear his name. It has cost £20,000, and was given to the Faculty by the Bloch Trust.

On Nov. 27, at the Faculty, 242, St. Vincent Street, Glasgow, C.2, at noon, Sir James Paterson Ross, Sir John Parkinson, Sir Alexander Boyne King, and Mr. Hugh Fraser will be admitted as honorary fellows. The biennial dinner will be held in the evening.

Medical Research Council

The period for receiving applications for the travelling fellowships in medicine mentioned in our issue of Sept. 5 (p. 300) has been extended until Nov. 10.

Association of Anæsthetists of Great Britain and Ireland

The annual meeting of this Association at Stratford-upon-Avon on Oct. 22 and 23 was attended by 300 fellows and members, some of whom came from Denmark, Iran, Malaya, the Netherlands, Portugal, South Africa, Sweden, and the United States. Dr. W. Grey Walter gave the John Snow lecture. The Dowager Marchioness of Reading was the guest of honour at the annual dinner, at which Dr. Ronald Jarman, the president, was in the chair.

National Hospital, Queen Square

This hospital will be celebrating its centenary next year from June 20 to 25. Further information may be had from Dr. Macdonald Critchley, The National Hospital, Queen Square, London, W.C.1.

Tuberculosis Hospital Closes

Within the next few weeks Basford Hospital, near Nottingham, which has 60 beds, will close as a tuberculosis treatment centre. After reconstruction it will reopen as a hospital for the elderly and chronic sick.

New Hospital at Swindon

On Oct. 24 Sir George Schuster, chairman of the Oxford Regional Hospital Board, opened the first stage of the Princess Margaret Hospital at Swindon. It is expected that when completed the whole hospital will cost over £2 million and will have 600 beds. The present building, which has cost £660,000, includes the outpatient and casualty departments, orthopædic ward, and physiotherapy and pathology departments of the whole hospital. Sir George Schuster said that it was hoped to start the second stage of the scheme next year. It would be a multi-storey building with more than 300 beds, a psychiatric ward, a postoperative recovery ward, and small hostels with gardens for nurses. The third stage of the plan would include an obstetric unit, a child-specialist unit and nurseries, and wards for old and chronic sick people.

British Orthopædic Association

At a dinner given by the Association in London on Oct. 23, Mr. Norman Capener, the president, announced that Queen Elizabeth the Queen Mother had agreed to be the patron. Mr. Derick Heathcoat Amory said that as Minister of Pensions he had received much help from orthopædic surgeons in dealing with the war-disabled; but perhaps the greatest appeal of orthopædics was in its work for children. He recalled that long ago children with deformed limbs and restricted movements were a common sight: amid the social and scientific revolution no change had been more encouraging than the improved health of children. Mr. Capener, responding to the toast of The Association, drew attention to the risk of over-preoccupation with techniques, and declared that no one system could be separated from others. The great needs of orthopædics—as of other branches—were better organisation, specially trained staffs, and proper facilities: they needed better hospitals. Mr. F. W. Holdsworth proposed The Guests, and Mr. N. J. Skelhorn, Q.C., responded.

Fulbright Travel Grants

Travel grants will again be available next year to citizens of the United Kingdom to go to the United States of America for academic or educational purposes. Full particulars may be had from the United States Educational Commission in the United Kingdom, 71, South Audley Street, London, W.1.

Anglo-French Exchange Bursaries

Applications are invited for bursaries to be awarded in 1960 to young British doctors under the exchange scheme arranged by the French Embassy in London between the Institut National d'Hygiene in Paris and the Ciba Foundation in London.

The grants (87,000 francs a month) will be awarded for two to four months to medical men who wish to obtain clinical experience or carry out research in France. Application forms may be had from Dr. G. E. W. Wolstenholme, director of the Ciba Foundation, 41, Portland Place, London, W.1. The closing date for applications is Jan. 30, 1960.

Midland Nerve Hospital

This hospital, which is a neuropsychiatric unit of the United Birmingham Hospitals, has now left its old outpatient department and moved to new buildings on the inpatient site in Elvetham Road, Edgbaston.

It was opened in 1913 as an outpatient clinic, and readily established a link with the Queen's Hospital, which formed part of the Medical School. It is now an integral part of the United Birmingham Hospitals, drawing on the teaching group for medical and nursing staff and ancillary services. Outpatient and teaching facilities were expanded when a day hospital, known as the Philip Cloake Wing, was opened in January, 1958. This building provides accommodation for 20 patients and includes treatment rooms, consulting-rooms, laboratories, an occupational-therapy department, and a canteen. The Minister of Health has provided the funds for the new outpatient department. It contains four consulting-rooms (for psychiatric and neurological clinics and psychotherapeutic groups), changing-rooms, a waiting-hall, and administrative offices. It was formally opened on Sept. 28, by Mr. E. A. Norton, the chairman of the board of governors.

Society of Medical Officers of Health

The anxieties and misgivings which medical officers of health had felt concerning the inception and form of the National Health Service had proved premature; many of the problems that had occupied their attention in the past still needed their continuing vigilance; and opportunities for the preventive health services were now coming in abundance: Lord Cohen of Birkenhead thus reassured his hosts when he proposed The Society at the annual dinner in London on Oct. 23. Sir Arthur Porritt also spoke encouragingly when he replied for The Guests, cordially proposed by Dr. Mary Paterson. Sir Arthur confessed that, in his new role as chairman of the Medical Services Review Committee, he had learned what a medical officer of health really was, and that had been a stimulating experience. His committee had been at work for nine months, and many people thought that was a reasonable period in which to produce something; but their magnificent and thankless task would take them a long time yet. For three or four months they had deliberately gone round in small circles, and thereby " this group of prima donnas " had got to know each other and largely lost their sectional interests. The society's president for 1959–60 is Dr. J. Stevenson Logan, medical officer of health for Southend, and he replied to Lord Cohen's toast.

Dr. E. Neil Reid and Dr. John Smith have been appointed members of the reconstituted Scottish Food Hygiene Council.

The Council of Industrial Design are holding a doctor's waiting-room exhibition at the Design Centre, 28, Haymarket, London, S.W.1, from Nov. 2 to 28.

CORRIGENDUM: *A New Flocculation Test.*—In the article by Dr. G. K. Daikos and his colleagues (Oct. 3, p. 488) the second sentence of the last paragraph of the discussion was: " Sera giving positive results remained positive after extraction with ether or chloroform ." This should have read: " Sera giving positive results *became negative* after . . ."

Diary of the Week

NOV. 1 TO 7

Monday, 2nd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Psychosomatic Misconceptions.

Tuesday, 3rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Pathology.* Dr. G. F. Joplin, Dr. K. A. Jegatheesan, Dr. D. Aldis, and Dr. S. B. Rosalki: Enzyme Systems in Diagnosis.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. J. M. Mitchison: Life Cycle of Growing Cells.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. C. H. Edwards: Neurological Complications of Pregnancy, Labour, and Puerperium.

POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. E. H. Belcher: Detection and Measurement of Radiation and Radioisotopes.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. A. M. Jelliffe: Local Treatment with Radioactive Isotopes.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Prof. C. E. Lumsden: Functions of the Glia.

UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Prof. A. C. Lendrum: Vascular Damage in the Pulmonary Circulation.

Wednesday, 4th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. W. S. Mack: Klinefelter's Syndrome and other Genetic Defects.

ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine.* Dr. A. D. Morris: 'Sir' John Hill, M.D. (1717–1775).
8 P.M. *Surgery.* Dr. A. I. Spriggs, Prof. Gilbert Causey, Dr. Joseph Bamforth, Dr. R. O. K. Schade: Exfoliative Cytology in the Diagnosis of Malignant Disease.

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. S. C. Frazer: Acid-base Metabolism.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Laboratory Diagnosis of Fungous Infection.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Lynne Reid: Types of Emphysema.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. A. H. Humphry: The Australian Aborigine and the Flying Public Health Doctor.

ASSURANCE MEDICAL SOCIETY
5 P.M. (11, Chandos Street, W.1.) Dr. P. M. F. Bishop: Recent Advances in Endocrine Therapy and Their Influence on the Prognosis of Endocrine Disease.

MIDLAND MEDICAL SOCIETY
8.15 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Mr. Hedley Atkins: A Critical Review of Treatment of Carcinoma of the Breast.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. W. H. Lloyd: Value of the Voice in the Diagnosis of Myxœdema in the Elderly.

NORTH WESTERN THORACIC SOCIETY
5 P.M. (Aintree Hospital, Liverpool.) Dr. T. Lloyd Hughes: Clinical Findings of the M.M.R. Campaign in Liverpool, Mr. J. F. Dark, Dr. J. Pemberton: 1000 Bronchoscopies.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Street, Edinburgh, 2
5 P.M. Sir Kenneth Cowan: The Climate of Health. (John Matheson Shaw lecture.)

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street, Edinburgh.) Dr. W. A. Alexander: History of the Medico-Chirurgical Society of Edinburgh. (Valedictory address.)

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St. Vincent Street, Glasgow, W.2
5 P.M. Prof. C. F. W. Illingworth: Contributions to the Physiology of Digestion. (Burns lecture.)

UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. R. S. McNeill: Pulmonary Ventilation and Perfusion in Health and Disease.

Thursday, 5th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Prof. Alan Kekwick: On Adiposity. (Bradshaw lecture.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. H. W. Burge: Vagal Nerve Section in Chronic Duodenal Ulceration. (Hunterian lecture.)

UNIVERSITY OF LONDON
5 P.M. (1, Wimpole Street, W.1.) Prof. Victor Lambert: Malignant Disease of the Post Nasal Space. (Semon lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. G. Pontecorvo: Genetic Analysis via Somatic Cells.

POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. T. Alper, Dr. M. Ebert, Dr. R. H. Thomlinson: Biological Effects of Radiation—General Survey.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5 P.M. Prof. O. L. Zangwill: Sensory Deprivation in Animals and Man.

Friday, 6th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Otology.* Mr. R. G. Macbeth: Thoughts on the Eustachian Tube. (Presidential address.)
2.30 P.M. *Laryngology.* Mr. Myles Formby: The Maxillary Sinus. (Presidential address.)
5.30 P.M. *Anæsthetics.* Dr. Alfred Lee: Anæsthesia in Abdominal Surgery Yesterday and Today. (Presidential address.)
8.30 P.M. *Orthopædics.* Prof. R. Merle d'Aubigné (Paris): Treatment of Ununited Fractures of Neck of Femur.

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Prof. Roland Barnes: Cartilagenous Tumours of Bone.
4 P.M. Dr. Donald Hunter: Mistakes in Diagnosis.

Saturday, 7th

MIDLAND THORACIC SOCIETY
3 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Dr. D. A. Williams: Allergy and Asthma.

Appointments

CRAIG, C. A., M.B. Belf., D.P.H.: assistant M.O. and school M.O., West Riding of Yorkshire (Todmorden division).

GUNSTENSEN, ENDRE, M.B. Edin.: ophthalmologist (S.H.M.O.), Royal Infirmary, Edinburgh.

HAUGHIE, R. G., M.B. Glasg., D.P.H.: assistant M.O.H. and school M.O., Bolton.

HOWARD, J. D., M.B. Sheff., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, United Sheffield Hospitals and Sheffield Regional Hospital Board.

MARTIN, V. D. R., M.B. Aberd., D.P.H.: M.O.H. and schools M.O., Doncaster.

MICHELL, GUY, M.B. Cantab., M.R.C.P., D.C.H.: part-time consultant child psychiatrist, department for children and parents, Tavistock Clinic, London.

MILLAR, I. B., M.D. Belf., D P.H.: senior M.O., Essex.

PIOTR, W. A., Med. Dipl. Poznan: senior casualty officer, Llwynypia Hospital, Glamorgan.

REGESTER, P. T., M.R.C.S., D.P.H.: deputy M.O.H. and deputy principal school M.O., Warrington.

ROBSON, P. N., M.B. Durh., F.R.C.S.: consultant orthopædic surgeon, Royal Victoria Infirmary, Newcastle upon Tyne.

ROSENTHAL, F. F. D., M.D. Lond., M.R.C.P.: part-time consultant physician, Leicester General Hospital.

SCOTT, D. B., M.D. Edin., F.F.A. R.C.S.: consultant anæsthetist, Royal Infirmary, Edinburgh, and Roodlands Hospital, Haddington.

Birmingham Regional Hospital Board:

BAIRD, R. B., M.B. Edin., M.R.C.P.E.: consultant pathologist, Walsall hospital group.

HAMILTON, J. G., M.D. Lond., M.R.C.P., F.R.C.S.: part-time consultant neurosurgeon, Stoke on Trent and West Bromwich hospital groups.

PRICE, E. W., M.B. Cantab., F.R.C.S.E., D.T.M. & H.: consultant bacteriologist, Birmingham (Selly Oak) hospital group.

East Anglian Regional Hospital Board:

DAVISON, WILLIAM, M.B. Edin., M.R.C.P.E.: consultant physician in geriatrics, Regional Board hospitals and United Cambridge Hospitals.

HENDERSON, G. D., M.B., B.SC. Otago: registrar in obstetrics and gynæcology, Peterborough group of hospitals.

MOORE, Q. S., M.B. Edin.: radiological registrar, Norfolk and Norwich Hospital.

RAPIDIS, P., M.D. Athens: registrar in psychiatry, St. Andrew's Hospital, Norwich.

ROXBURGH, R. C., M.D. Cantab., M.R.C.P., D.C.H.: consultant pædiatrician, West Norfolk and North Cambridgeshire area hospitals.

WEDGWOOD, JOHN, M.D. Cantab., M.R.C.P.: consultant physician in geriatrics, West Suffolk hospital group.

South-Western Regional Hospital Board:

BRADBEER, T. L., M.B. Lond., F.R.C.S., D.L.O.: consultant E.N.T. surgeon, Devon and Exeter clinical area.

CANNICOTT, S. M., M.B. Cantab., D.P.M.: assistant psychiatrist, Mendip Hospital, Wells.

LLOYD, T. W., D.M. Oxon., M.R.C.P.: consultant physician/geriatrician, North Gloucestershire clinical area.

TEMPLETON, ANN, M.B. Glasg.: assistant medical director, mass radiography services, Devon and Cornwall.

VALENTINE, M. G., M.D. Aberd., D.P.M.: consultant psychiatrist, Bristol mental hospitals.

WALKER, D. L., M.D. Lond., D.P.M.: consultant psychiatrist/medical superintendent, Horton Road and Coney Hill group of hospitals.

WEEKS, MARY M., M.B.: assistant geriatrician, West Cornwall clinical area.

Colonial Appointments:

BOWMAN, WILLIAM, M.B. Durh.: M.O., Sierra Leone.

BOYLAN, MARY T., M.B. Belf.: M.O., Somaliland.

DUNCAN, MACADAM, M.B. Glasg.: M.O., Northern Region, Nigeria.

DYRTING, A. E., M.D. Copenhagen: M.O., British Guiana.

GRAHAM, A. C., M.B. Lond., D.C.H.: medical registrar, Barbados.

LLOYD, H. J., M.B. Cantab.: M.O., Seychelles.

LYNCH, K. J. B., M.B. N.U.I.: M.O., South Cameroons, Federation of Nigeria.

VILAIN, P. B., L.R.C.P.E.: house-officer, health department, Trinidad.

WATT, A. C., M.B. Edin.: M.O., North Borneo.

Births, Marriages, Deaths

BIRTHS

ELLIS.—On Oct. 22, at the Radcliffe Infirmary, Oxford, to Wendy, wife of Harold Ellis, F.R.C.S., a son—Jonathan Richard.